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A STUDY OF THE CORPORA LUTEA AND THE ENDOMETRIUMS IN PATIENTS WITH UTERINE FIBROIDS*

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INTRODUCTION

THE etiology of uterine fibroids is unknown. The most generally accepted theory at the present time proposes the etiologic importance of estrin. Excessive stimulation of the myometrial tissues by either hyperestrinism or the unopposed action of estrin results in this tumor formation according to many authors. Proof given to establish this theory consists of both experimental and clinical facts and interpretations.

Clinically, the existence of a close relationship between ovarian function and the development of uterine fibroids has been accepted. This conclusion was based upon the following:

1. Fibroids develop only during active ovarian life.
2. Fibroids usually cease to grow after the menopause or after castration.
3. Fibroids grow rapidly during pregnancy.
4. Sterility in patients with fibroids is thought to be dependent upon disturbed ovarian function (Freund, 1913; Albrecht, 1928).
5. Abnormal uterine bleeding is a common symptom of patients with fibroids. The bleeding is considered to be the result of ovarian dysfunction (Graves, 1930).
6. Cystic glandular hyperplasia has been reported frequently in such patients. Hyperplasia results from excessive or prolonged estrogenic stimulation. Thus, estrin

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has been considered the common etiologic factor (Witherspoon, 1933 and 1935, and others).

7. Failure of ovulation has been reported by many (Witherspoon, 1933; Burch and Burch, 1933; Albrecht, 1935; and Popow, 1890).

8. The frequent finding of multiple follicular cysts in the ovaries has suggested the possibility of excessive estrin production (Witherspoon, 1933; Burch and Burch, 1933; Albrecht, 1928; Popow, 1890).

9. Endometriosis and adenomyosis are frequent concomitant lesions with uterine fibroids. Since these lesions occur only during the active life of the ovaries, the importance of the ovarian hormone as a common etiologic agent is assumed (Smith, 1929; Allen, 1933; Witherspoon, 1935).

It must be noted here, however, that most of the above statements have been subjected to criticism.

R. Meyer (1930) believed that the growth of fibroids was dependent on the ovary, principally because active ovarian function was associated with increased blood supply to the pelvic tissues. Dichtl (1938) demonstrated that fibroids might grow after the menopause in the presence of extensive vascular adhesions. The rapid growth of fibroids during pregnancy is, in many instances at least, not a true growth but rather an enlargement due to edema, degenerative changes, and increased blood supply. R. Meyer (1930) stressed the fact that many patients with fibroids menstruated and ovulated normally and became pregnant. Cystic ovarian changes were present in no unusual frequency in patients with fibroids (Häggstrom, 1932). Curtis (1938) suggested that the sterility was dependent upon an interference with the development and delivery of the fetus rather than the prevention of conception.

Experimentally, it has been reported that fibromyomas have been produced in the guinea pig as a result of the administration of large doses of estrogens over a long period of time (Nelson, 1937; Dessau, 1938; Moricard and Cauchoix, 1938; Lipschutz and Iglesais, 1938). Lacassagne (1935) reported that he was able to produce myometrial fibromas in the rabbit by prolonged administration of the estrogenic hormone. In all other experimental animals such as the mouse, rat, and monkey all efforts to produce fibroids have failed.

The foregoing remarks indicate that estrin, as a single etiologic factor, may be very important, but that, as yet, definite proof has not been established.

The study reported in this paper was undertaken to give the authors a personal knowledge of the ovarian function and endometrial relationship in 100 unselected and consecutive patients operated upon for uterine fibroids.

MATERIAL AND METHODS

This study is based upon two extremely important facts; namely, that preparations and plans were completely thought out before the collection of specimens was begun, and that the patients were unselected and consecutively operated upon. There was no attempt made to choose the time of the cycle at which to operate upon the patients. In this way, the study more truly portrays the actual findings in 100 patients with uterine fibroids.

It was decided that 100 specimens of uterine fibroids with histologic preparations of the endometria and the ovaries would be adequate material and that more than this number would make the material too unwieldy to study individually and personally with the maximum efficiency. The collection of specimens required one year's time.

One of us or our assistant, Mrs. Laird, was required to be present at each operative procedure. A description of the operative findings was written at once. The number, position, and size of the fibroids, size of the ovaries and the character of

the follicles, corpora lutea, and the concomitant pelvic pathology were recorded. Several blocks of endometrium from various portions of each uterus were fixed in aqueous-formol-chrome-sublimate. Portions of the corpora lutea were fixed in aqueous-formol-chrome-sublimate and various other fixations for cytologic studies. The tissues were embedded in paraffin and cut at five microns. Mallory connective tissue stain and acid fuchsin-methyl green stain were used.

Throughout the study, only the functioning corpus luteum of the cycle that is being observed will be considered and counted. Many patients had a corpus luteum of the immediately preceding cycle, but they are not to be considered, because of our desire to rigidly limit the study to the present cycle as nearly as possible.

The cytologic descriptions will be published later. All tissues were fixed within five minutes after the blood supply was clamped. In some instances, the ovary containing the corpus luteum was not removed but the corpus luteum was dissected out for histologic study.

An accurate menstrual history was obtained from each patient, and when some doubt existed, the menstrual dates were checked again immediately. In this manner, a survey of hospital records months afterwards was obviated.

The 100 patients ranged in age from 26 to 52 years. Four were from 26 to 29 years of age, eight from 30 to 34, thirty-eight from 35 to 39, twenty from 40 to 44, twenty-six from 45 to 49, and four from 50 to 52 years of age.

The patients were grouped according to the character of their menstrual cycles. Twenty-two patients had no variation from their normal cycles (Fig. 1). In all of these patients the menstrual cycles were within the limits given for normal. Twenty-six patients complained of menorrhagia. Fifteen of these had such a slight increase in flow that the cycles were still within normal limits. For this reason they are considered as a separate group (Fig. 2). Eleven patients had menorrhagia sufficiently severe to disturb their usual menstrual rhythms (Fig. 3). The menstrual history of Patient 46, for example, appears within normal limits in Fig. 3. The flow of four days' duration was characterized by the patient as a hemorrhage which was at variance with her previous normal period. For this reason she is considered in this group. In other instances the charts of patients with irregular and abnormal bleeding indicate that the present cycle is normal. As nearly as possible, the data presented in the charts are those of the single menstrual cycle about the time of operation. It is frequently observed that a patient with abnormal bleeding may have a completely normal cycle interspersed with an abnormal cycle. Thus, while the single cycle studied and charted may be normal, the patient is grouped according to the predominant type of bleeding complained of.

A group of 8 patients complained only of metrorrhagia (Fig. 4). Thirty-five patients had both metrorrhagia and menorrhagia (Fig. 5). Amenorrhea, partial or complete, was present in four patients. One patient had oligomenorrhea. Three patients were pregnant at the time of operation and one other patient had a chorioepithelioma. Each group will be studied and discussed individually.

GROUP I. NORMAL MENSTRUATION

The 22 patients in this group ranged in age from 29 to 46 years (Fig. 1). The average age was 39 years. Concomitant pelvic pathology was present in 13 patients (residues of pelvic infection, 5; bilateral dermoid cysts, 1; papillary cystadenoma, 1; and endometriosis, 6). Only one patient possessed ovaries with follicular cysts. The largest was 2 cm. in diameter and only 3 were present. The ovaries of the patients in this group were normal in size, except in the instance of the patient with the dermoid cysts.

Seven of the 22 patients were sterile. Three had no pelvic pathology other than the fibroids, while 2 had residues and 2 had endometriosis. One of the 22 patients had never married and had had no pregnancies.

Ten patients had had 23 full-term pregnancies and 3 miscarriages. Four patients had been pregnant but had never completed full-term pregnancies.

Eight patients of this group were operated upon on or before the fourteenth day of their cycles (Fig. 1). There was a corpus luteum of the present menstrual cycle

in only one instance and that was in a patient operated upon on the fourteenth cyclic day (Patient 9). The corpus luteum was young. The granulosa cells were not completely luteinized. There was a very meager amount of connective tissue in the granulosa cell layer. A connective tissue lining of the central cavity was absent. The theca cells contained many vacuoles from which lipoids had been dissolved during the process of fixation. The endometrium was early progravid.

Several patients had demonstrable degenerating corpora lutea of the immediately previous cycle and some had large mature follicles. The endometriums in the patients without corpora lutea were proliferative in type and were similar to the endometria removed at similar times in the cycle from normal women and *Macacus rhesus* monkeys (Bartelmez, 1933; Markee, 1936). There was no cystic glandular hyperplasia present.

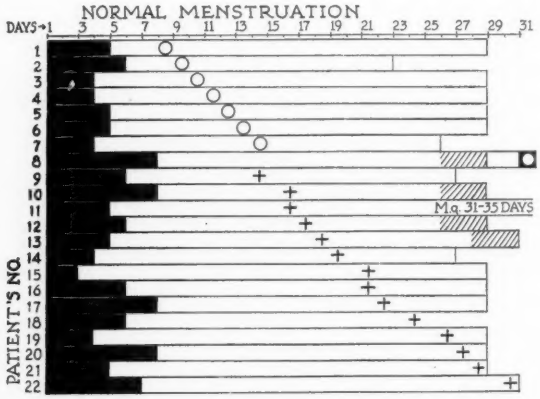

Fig. 1.

Figs. 1 to 5.—In all the charts the days of the menstrual cycle are arranged horizontally. The patients' numbers are listed vertically. The last menstrual cycle of each patient is portrayed in the horizontal columns. The solid black portion represents the bleeding phase of the cycle. In those patients operated upon before the menstrual flow has ceased, the solid black portion indicates the usual anticipated length of flow. The terminal bar at the end of the column indicates the length of the menstrual cycle. The diagonal lines indicate the variability in the length of the cycle in an individual patient. The zero indicates both the day of the menstrual cycle the patient was operated upon, and the absence of a functioning corpus luteum of the present cycle. The plus sign indicates the presence of a functioning corpus luteum of the present cycle as well as the day of the cycle the patient was operated upon.

Fourteen patients were operated upon after the sixteenth day of the cycle (Fig. 1). Thirteen had functioning corpora lutea of the present cycle. One patient (Patient 8, aged 44 years) without a corpus luteum was operated upon on the thirty-first day of her cycle, just as menstruation was beginning. The endometrium was proliferative in type and some desquamation had occurred. A corpus luteum could not be demonstrated grossly. Tissues were available for microscopic study from only one ovary. It is probable that this represents an instance of cyclic anovulatory bleeding, but one cannot prove this, since both ovaries were not sectioned serially.

The corpora lutea in the two patients (Patients 10 and 11) operated upon on the sixteenth day differed in degree of development. One (Patient 10) was typical of the early vascularization stage, while the other was distinctly younger (Patient 11). The endometrium of Patient 10 showed the greater degree of stimulation. It is interesting to compare the menstrual histories of the 2 patients. The cycle of Patient 11 was thirty-one to thirty-five days as compared to that of Patient 10 which was twenty-six to twenty-eight days. Ovulation had undoubtedly taken place later in the cycle in that patient with the longer cycle. This is consistent with the phenomenon as it occurs in entirely normal women.

The corpora lutea removed on the seventeenth and eighteenth days of the cycles, respectively (Patients 12 and 13), were in the vascularization stage. The endometriums were early progravic in character.

All of the corpora lutea removed after the nineteenth cyclic day were in the so-called bloom stage. The endometrium in each instance evidenced the normally anticipated degree of stimulation. In Patient 15 the corpus luteum was 3 cm. in diameter and was cystic. The characteristic folds of the walls were absent. The cells appeared normal in all respects. The endometrium was normally stimulated. The cystic condition of the corpus luteum had apparently not altered its normal physiologic function.

Patient 21 was operated upon on the twenty-eighth day. Her normal cycle was twenty-eight days in length. The late progravid endometrium had not evidenced any involution, and menstruation was not imminent. The corpus luteum showed no signs of disintegration and was in a typical bloom stage. This cycle, while normal, was to be of greater length by several days than the usual.

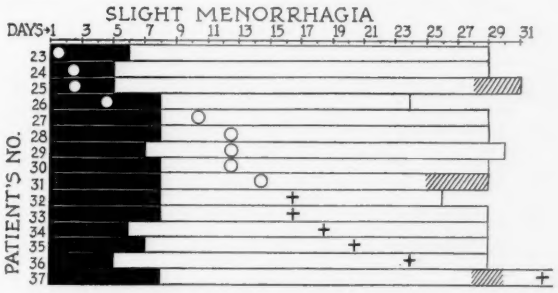

Fig. 2.

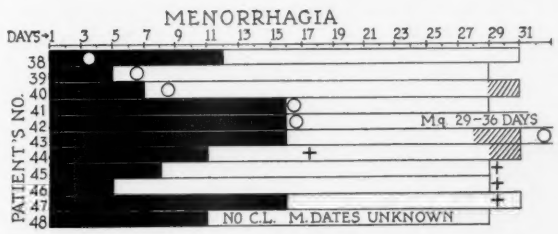

Fig. 3.

Patient 22, operated upon on the thirtieth day of her usual thirty-day cycle, possessed an endometrium in which involution had begun. The edema had largely disappeared and the glands were collapsed. There was a broad compacta filled with typical decidual cells. Such decidua may occur in the normal endometrium in the absence of pregnancy. The granulosa lutein cells were markedly degenerated in some portions, while in others the cells were typical of the late bloom stage. The corpus luteum was apparently undergoing degenerative changes prior to and more rapidly than the endometrium was evidencing the disintegration which typifies menstruation. This finding is consistent with that observed in the tissues of normal women.

The endometrium of Patient 18, removed at the end of the twenty-fourth cyclic day, showed beginning slough (Fig. 6). This patient's cycle was twenty-four days in length. The corpus luteum was degenerated for the most part (Fig. 7) but some small portions were still in the stage of bloom (Fig. 8).

The regression of the corpora lutea in Patients 18, 21, and 22 was of various degrees. It was more extensive in Patient 18 than in Patients 21 and 22, although

the corpus luteum was removed earlier in the cycle in the case of the former. Desquamation of portions of the endometrium had occurred while the endometrium in Patients 21 and 22 evidenced involution in one instance and a late progravid stage without involution in the other. The close relationship between the character of the corpus luteum and the changes in the endometrium as noted here is identical to that observed in the tissues of normal women.

Fig. 4.

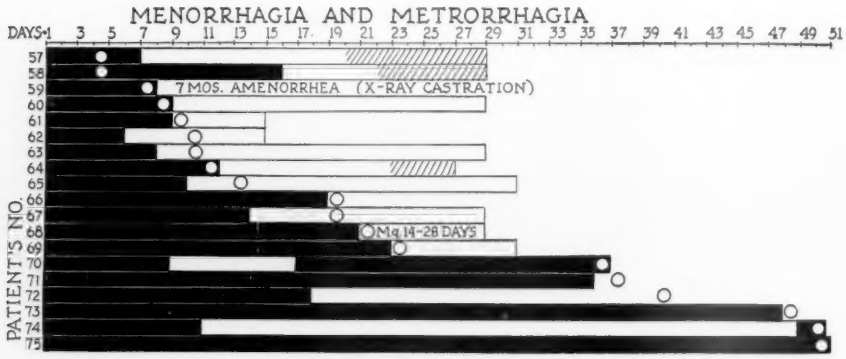

Fig. 5, *A*.

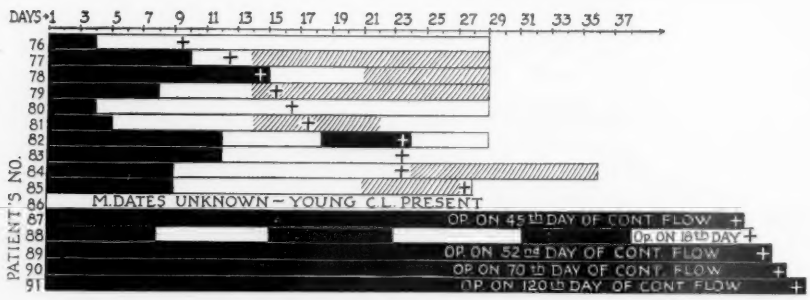

Fig. 5, *B*.

Such findings suggest strongly that there is no disturbance in the ability of the follicle and the corpus luteum to stimulate the endometrium normally and the endometrium to respond normally in this group of patients with uterine fibroids. The endometriums showed no hyperplasia or any undue or abnormal estrogenic stimulation.

Ovulation had occurred and the development of the corpus luteum through its life cycle had progressed similarly in all instances to these phenomena as they occur in normal women.

GROUP II. SLIGHT MENORRHAGIA

The 15 patients of this group complained of a menorrhagia so slight that it did not alter the cycles beyond the accepted limits of normal (Fig. 2). Their ages ranged from 26 to 49 years with an average age of 43 years. Concomitant pelvic pathology was present in eight instances (residues 7, and endometriosis 1). Three patients had never been married and twelve were married. Three of the 12 patients had never been pregnant, and in each, residues of pelvic infection were present which might have accounted for their sterility. Nine of the 12 who had become pregnant had completed 18 full-term pregnancies and only 1 had had a miscarriage.

The ovaries were of normal size in all but 3 patients of this group (Patients 23, 30, and 37). The cysts that produced the enlargements were follicular in 2 patients and a cyst of the corpus luteum in the other (Patient 37).

Nine of the 15 patients comprising this group were operated upon on or before the fourteenth day of the menstrual cycle. None possessed functioning corpora lutea of the present cycle. In most instances, corpora lutea of the previous cycle were identified.

The endometrium in each instance was stimulated to the degree that is considered normal for the stage of the cycle in which the tissue was removed. No cystic glandular hyperplasia was present.

Six patients were operated upon after the fourteenth day. In each a histologically normal corpus luteum was present. That the corpora lutea were functioning normally was indicated by the degree of the stimulation of the endometrium. The usually accepted normal relationship between the endometrium, the ovarian follicles, and corpus luteum existed here. Some slight variation was present in the tissues of Patient 37. This patient's usual cycle was twenty-eight to twenty-nine days in length. In the present cycle, however, she had failed to menstruate at the expected time and had not yet begun to flow when she was operated upon on the thirty-second day. The endometrium was early progravid. The corpus luteum was 2.5 cm. in diameter and the folds were not as prominent as usually observed. The cells, however, were histologically normal. The stage of the corpus luteum was typical of an early bloom phase. The degree of stimulation of the endometrium was consistent with the extent of the development of the corpus luteum. Such findings might represent an instance of ovulation occurring late in the cycle. All the histologic evidences found in these tissues indicate them to be within normal limits, both anatomically and physiologically.

In this group of 15 patients with slight menorrhagia, the findings reduplicated those observed in the first group of normally menstruating patients and in normally menstruating patients without any pelvic pathology. In no instance in either of the groups did the character of the endometrium and the ovarian findings indicate any evidence of excessive, prolonged, or unopposed estrogenic stimulation.

There was no failure of ovulation in any of these patients. The corpora lutea were normal and the endometriums had responded to corpus luteum stimulation in a normal manner. No so-called glandular hyperplasia was present. There was no disturbance from the normal in the ovarian and endometrial relationships in these patients.

GROUP III. MENORRHAGIA

Eleven patients complained of menorrhagia severe enough to disturb their menstrual rhythms (Fig. 3). In many instances normal cycles were interspersed among the abnormal ones. The ages of these patients ranged from 35 to 49 years, with an average age of 39 years. Concomitant pelvic pathology was present in 9 of the 11 patients (residues, 6; endometriosis, 1; endometriosis and residues, 1; parovarian cyst, 1). Follicular cysts were present in the ovaries of 4 patients. The largest was 6 cm. in diameter and in the other instances the measurements were 4, 2, and 2 cm., respectively. The sizes of the ovaries containing these cysts were only slightly greater than normal, with the exception of the one containing the 6 cm. cyst. The ovaries of the remaining patients were normal size.

Ten of the 11 patients were married. Four had never been pregnant. Two of these patients with sterility had residues of pelvic infection, one had endometriosis,

and the other had a small parovarian cyst. The sterility might readily have been the result of the concomitant pathology rather than the fibroids, since these pathologic lesions preceded the fibroids by many years.

Five patients had 21 pregnancies. Twelve terminated by full-term deliveries and 9 resulted in miscarriages. One of the 11 patients had never delivered a full-term pregnancy but had had 5 miscarriages.

It is in this group of patients with abnormal bleeding that some irregularities in the normal cyclic behavior of the ovaries and endometriums were observed. Patient 41 and patient 42, operated upon on the sixteenth day just at the termination of fifteen days of bleeding in each instance, possessed no corpora lutea of the present cycle. That ovulation would not have occurred during this cycle, however, cannot be stated, since there is a large, normal, mature follicle in one ovary of each patient. The endometrium in each instance was of an immediately postmenstrual type.

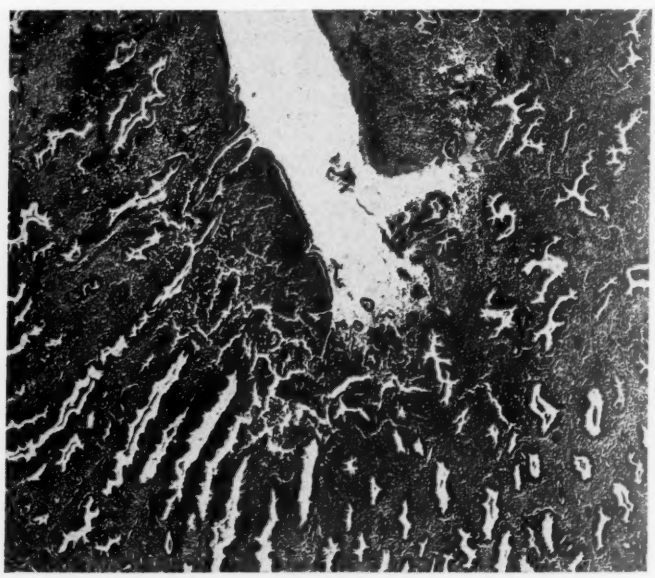

Fig. 6.

Figs. 6, 7, and 8.—Patient 18. Twenty-four-day cycle. Patient was operated upon as flow was beginning. Early desquamation of a small portion of the endometrium is shown. In Fig. 7 marked degeneration of the granulosa lutein cells is evident. Theca lutein cells are indicated by the arrow. Portions of the granulosa lutein cells had not undergone regression (Fig. 8). This demonstrates that the relationship between the corpus luteum and the endometrium is normal.

Patient 43 was operated upon on the thirty-second cyclic day. The usual cycle was twenty-eight to thirty days in length. No bleeding had occurred, however, and there was no indication found in the endometrium that menstruation would occur in the near future. The endometrium was a normal, proliferative type. The ovaries contained no corpus luteum. This patient, aged 49 years, had had two short periods of amenorrhea in the two years preceding the operation. Although she had no hot flushes, the amenorrhea and her age suggest an approaching menopause which might account for the failure of ovulation.

Patient 48 could give no dates concerning her menstrual periods. The ovaries contained no corpus luteum, and the endometrium was a proliferative type.

All of the remaining patients of this group had ovarian and endometrial findings that were consistent with those considered normal for the time of the cycle in which they were operated upon.

GROUP IV. METRORRHAGIA

Eight patients complained of metrorrhagia (Fig. 4). No variations in the length of their cycles had occurred. The metrorrhagia was not present in every cycle, but the patients were placed in this group because metrorrhagia was complained of during the few months prior to operation. The ages ranged from 35 to 52 years, with an average age of 42 years at the time of operation.

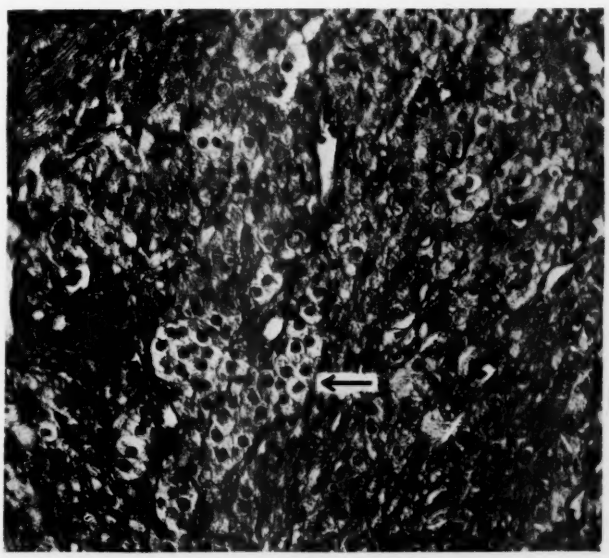

Fig. 7.

Fig. 8.

Three patients had concomitant pelvic pathology (residues of pelvic infection, 2; endometriosis, 1). The ovaries of the 8 patients were normal in size and in none were there any follicular cysts.

Two of the 8 had never been married. Two patients had had no pregnancies. Of these 2, one had endometriosis and the other had no concomitant pelvic pathology. Two patients had completed 2 full-term pregnancies. The remaining 2 patients had been pregnant four times but each pregnancy had terminated by a miscarriage.

The 2 patients operated upon on the second day of the menstrual flow had degenerating corpora lutea and were menstruating from a previously prepared, normal, progravid endometrium. The other patients, with the exception of Patient 53, showed completely normal ovarian and endometrial relationship (Fig. 4). That a patient 50 years of age (Patient 53) should fail to ovulate and menstruate on the expected day is not distinctly abnormal.

The ovarian and endometrial findings in these patients are consistent with those in normal women. The single cycles studied in these patients were relatively normal, although a history of metrorrhagia occurring in some cycles was obtained from each patient.

GROUP V. MENORRHAGIA AND METRORRHAGIA

There were 35 patients who had both menorrhagia and metrorrhagia. Their ages were from 31 to 47 years with an average age of 40 years at the time of operation. Concomitant pelvic pathology was present in 20 of these patients (residues of pelvic infection, 14; endometriosis, 4; residues and endometriosis, 1; parovarian cyst, 1).

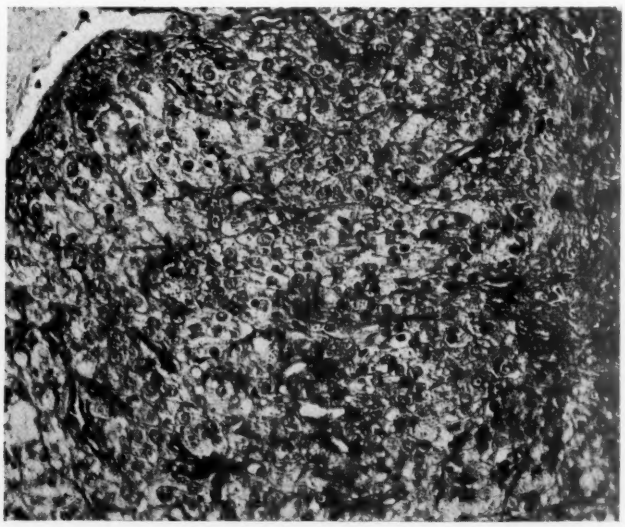

Fig. 9.

Figs. 9, 10, and 11.—Patient 78. Bleeding which began as a regular menstrual period had continued for fourteen days when the patient was operated upon. A portion of the corpus luteum in the regression phase is shown in Fig. 9. Fig. 10, taken at the same magnification, shows granulosa lutein cells typical of the bloom stage. The endometrium shown in Fig. 11 has a denuded surface. The endometrial glands are secretory in type in some portions of the endometrium and in others are typical of a proliferative stage (arrows). These figures demonstrate irregular regression of the corpus luteum and the associated shedding of the endometrium.

Follicular cysts were present in the ovaries of 9 patients. In 2, the cysts were 6 and 8 cm. in diameter, respectively. In the others the cysts were 2 cm. or less in size. A 5 cm. corpus luteum cyst was present in one instance (Patient 89). The size of the ovaries in the remaining patients of this group were normal.

Two patients had never married and had had no pregnancies. Seven patients had never been pregnant. One had residues of pelvic infection, 3 had endometriosis, and 3 had no concomitant pelvic pathology.

Twenty-six patients had been pregnant. Nineteen of these had completed 40 full-term pregnancies and had also had 9 miscarriages. Seven of the 26 patients who had been pregnant failed to carry a pregnancy to term and had had 18 miscarriages.

Nineteen of the 35 patients in this group had no corpora lutea of the present cycle (Fig. 5, *A*). Several, however, had normal corpora lutea of the previous cycle

in stages of regression (Patients 57 and 58, for example). Although these findings are not used in this paper, they do indicate that ovulation and corpus luteum development had occurred in the previous cycle.

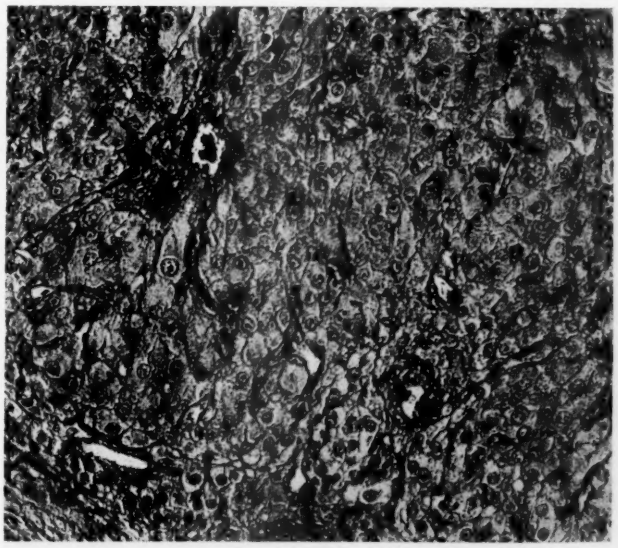

Fig. 10.

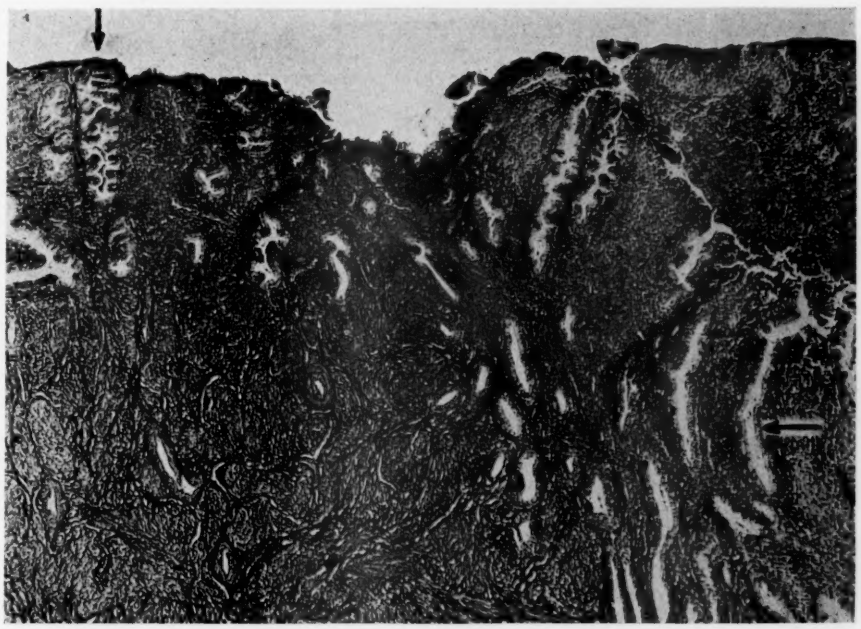

Fig. 11.

Patient 59 had a seven-month period of amenorrhea following x-ray therapy. The menstrual flow at the time of operation was scant. The endometrium had sloughed in portions and in others was low and atrophic. There was no sign of previous stimulation by the corpus luteum hormone.

Patient 74, aged 43 years, was operated upon on the second day of flow, following a cycle of fifty days in length (Fig. 5, *B*). The endometrium was proliferative in type without evidence of previous progravid character and had desquamated to a moderate extent. No corpus luteum was found.

In this group of patients without functioning corpora lutea of the present cycle, there was cystic glandular hyperplasia of the endometrium in only one instance (Patient 73). The hyperplasia was not marked.

Sixteen patients who complained of menorrhagia and metrorrhagia had corpora lutea. Of the 35 patients with menorrhagia and metrorrhagia, approximately half had corpora lutea, irrespective of the bleeding. In many instances the patients were operated upon during a relatively normal cycle (Patients 76, 79, 80, 81, 84, 85, and 88). In these patients the appearance of and the relationship between the corpora lutea and the endometriums were normal. Similar normal findings and relationship existed in some of the patients with abnormal cycles (Patients 77, 82, and 83).

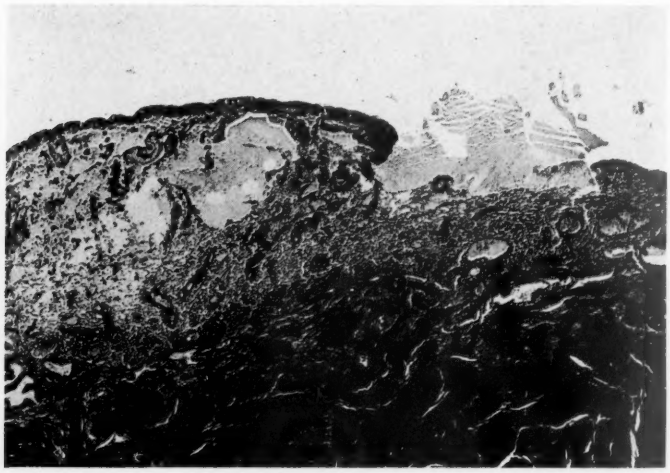

Fig. 12.

Figs. 12, 13, and 14.—Patient 87 had continuous bleeding for forty-five days. The endometrium pictured in Fig. 12 shows a localized region of disintegration and slough, adjacent to which is a region showing response to corpus luteum stimulation. It is not entirely normal, however. In other portions of the uterus the endometrium is typical of the proliferative phase (Fig. 13). In Fig. 14 the corpus luteum obtained from this patient is characteristic of the "bloom" stage. It is normal histologically. These findings suggest that the end organ (endometrium) is unable to respond in a normal manner to corpus luteum stimulation.

Patient 76 who was operated upon on the ninth day had a normal corpus luteum in the vascularization stage. Ovulation must have preceded operation by at least three or four days. Thus, in this patient ovulation occurred on or about the sixth day. Ovulation early in the cycle has been observed occasionally in normal women. The endometrium was progravid in character and consistent with the degree of development of the corpus luteum.

Irregular shedding of the endometrium occurred in Patient 78 (Table I). The granulosa lutein cells of the corpus luteum, removed on the fourteenth day of the present cycle, had undergone regression in some regions (Fig. 9), but in others the cells were typical of the bloom stage (Fig. 10). Active functioning cells such as these are not normally present in a regressed corpus luteum of the previous menstrual cycle. The endometrium had desquamated in most regions but the progravid character was still discernible (Fig. 11). It is probable that the irregular shedding of the endometrium was due, in this instance, to irregular regression of the corpus luteum.

In 4 patients (Patients 87, 89, 90, and 91) several unusual findings were observed. Patient 87 had been bleeding continuously for forty-five days. A small portion

of the endometrium in the process of desquamation is shown in Fig. 12. Adjacent to this, the endometrium was progravid in character, but it was not completely normal. Stimulation by the corpus luteum hormone is present, however. In other regions the endometrium is much thicker and is in the proliferative phase without signs of corpus luteum hormonal stimulation (Fig. 13). In the ovary, there is a histologically normal corpus luteum in the stage of bloom (Fig. 14). The explanation of such findings is not immediately apparent. It may be that our criteria for

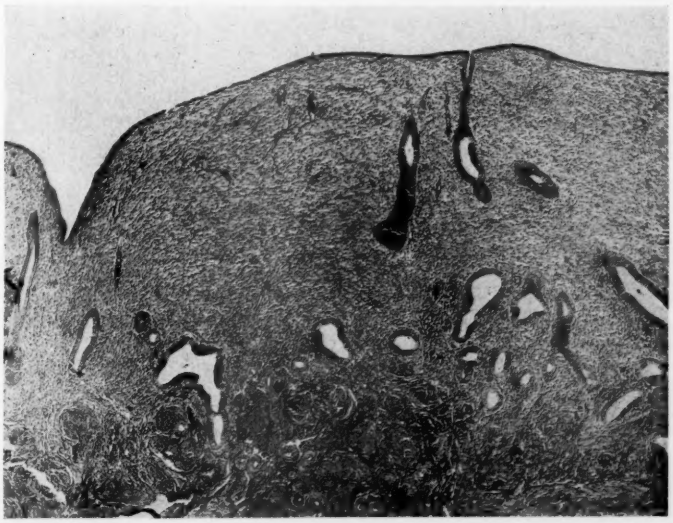

Fig. 13.

Fig. 14.

the diagnosis of a normal corpus luteum by histologic methods are inadequate. More logically, however, the explanation is to be found in the fact that the corpus luteum is normal and that the bleeding endometrium is incapable of responding in a normal manner.

In Patients 90 and 91, who had been bleeding continuously for some time (Fig. 5, *B*), the corpora lutea were normal and the endometriums were progravid. The

TABLE I. NORMAL MENSTRUATION

PATIENT	AGE	CONCOMITANT PELVIC PATHOLOGY	FUNCTIONING CORPUS LUTEUM	ENDOMETRIUM	DAY OF CYCLE OPERATED
		Normal Menstruation			
1	45	Residues	None	Resting	8
2	45	Adenomyosis	None	Proliferative	9
3	36	Residues	None	Proliferative	10
4	39	None	None	Proliferative	11
5	32	None	None	Proliferative	12
6	36	Residues	None	Proliferative	13
7	35	Residues	None	Proliferative	14
8	44	Uterine prolapse	None	Proliferative	1
9	37	Endometriosis	Young	Progravid	14
10	33	Endometriosis	Vascularization	Progravid	16
11	30	None	Young	Progravid	16
12	37	None	Vascularization	Progravid	17
13	46	Endometriosis	Vascularization	Progravid	18
14	46	Ovarian tumor	Bloom	Progravid	19
15	40	None	Bloom	Progravid	21
16	42	Endometriosis	Bloom	Progravid	21
17	45	None	Bloom	Progravid	22
18	29	Endometriosis	Regression	Menstruating Progravid	25
19	35	Ovarian tumors	Bloom	Progravid	26
20	46	None	Bloom	Progravid	27
21	29	None	Bloom	Progravid	28
22	46	Residues	Beginning Regression	Progravid Involution	30
		Slight Menorrhagia			
23	26	Perisalpingitis	None	Menstruating	1
24	36	None	None	Menstruating	2
25	46	None	None	Menstruating	2
26	45	Residues	None	Menstruating	4
27	42	Residues	None	Resting	10
28	39	Residues	None	Proliferating	12
29	36	None	None	Proliferating	12
30	47	Endometriosis	None	Proliferating	12
31	45	None	None	Proliferating	14
32	36	None	Young	Progravid	16
33	49	Endometrial polyp	Bloom	Progravid	16
34	36	Residues	Bloom	Progravid	18
35	45	Residues	Vascularization	Progravid	25
36	37	None	Bloom	Progravid	23
37	40	Residues	Bloom	Progravid	32
		Menorrhagia			
38	36	Residues	None	Menstruating	3
39	44	Endometriosis	None	Resting	6
40	39	None	None	Proliferating	8
41	38	None	None	Proliferating	16
42	37	Residues	None	Proliferating	16
43	49	Residues	None	Proliferating	32
44	41	Endometriosis Residues	Vascularization	Progravid	17
45	35	Residues	Bloom	Progravid Involution	29
46	35	Previous operation Residues	Bloom	Progravid	29
47	40	Parovarian cyst 2 cm.	Bloom	Progravid Involution	29
48	39	Residues	None	Proliferative	?

TABLE I—CONT'D

PATIENT	AGE	CONCOMITANT PELVIC PATHOLOGY	FUNCTIONING CORPUS LUTEUM	ENDOMETRIUM	DAY OF CYCLE OPERATED
		Metrorrhagia			
49	41	None	None	Proliferative	10
50	35	Residues	None	Proliferative	13
51	52	None	None	Menstruating Progravid	27 2
52	35	Residues	None	Menstruating Progravid	31 2
53	50	None	None	Proliferative	42
54	36	None	Bloom	Progravid	16
55	46	Endometriosis	Vascularization	Progravid	17
56	42	None	Bloom	Progravid	25
		Menorrhagia and Metrorrhagia			
57	36	Residues	None	Menstruating	4
58	34	Residues	None	Menstruating	4
59	38	Residues	None	Menstruating Atrophic	7
60	40	Endometriosis Residues	None	Menstruating	8
61	36	Endometriosis	None	Resting	9
62	45	Residues	None	Proliferative	10
63	47	Adenomyosis	None	Proliferative	10
64	38	None	None	Menstruating Proliferative	11
65	33	None	None	Proliferative	13
66	38	Residues	None	Resting	19
67	45	None	None	Resting	19
68	38	Parovarian cyst 12 cm.	None	Resting	21
69	40	None	None	Resting	23
70	39	Residues	None	Menstruating	36
71	45	None	None	Resting	38
72	44	None	None	Proliferative Polypoid	40
73	46	None	None	Proliferative Sl. hyperplasia	48
74	43	None	None	Menstruating	50
75	47	Endometriosis	None	Menstruating Resting	50
76	31	None	Vascularization	Progravid	9
77	47	None	Bloom	Progravid	12
78	36	None	Regression Bloom	Menstruating Progravid	14
79	37	Residues	Bloom	Progravid	15
80	40	Residues	Vascularization	Progravid	16
81	46	Residues	Vascularization	Progravid	17
82	43	Residues	Bloom	Progravid	23
83	34	Residues	Bloom	Progravid	23
84	39	None	Bloom	Progravid	23
85	40	Residues	Bloom	Beginning Menstruation	27
86	47	Endometriosis	Vascularization	Progravid	?
87	44	Residues	Bloom	Menstruating Progravid Proliferative	45
88	47	Endometriosis	Bloom	Progravid	18
89	46	Residues	Bloom	Progravid	52
90	43	None	Bloom	Progravid	70
91	36	None	Bloom	Progravid	120

TABLE I—CONT'D

PATIENT	AGE	CONCOMITANT PELVIC PATHOLOGY	FUNCTIONING CORPUS LUTEUM	ENDOMETRIUM	DAY OF CYCLE OPERATED
			Oligomenorrhea		
92	37	Residues	None	Proliferative	18
			Amenorrhea		
93	37	Residues	None	Proliferative	12
94	41	None	Vascularization	Progravid	39
95	52	Endometriosis	None	Proliferative	47
96	51	Pyometria	None	Resting	11 yr.
			Pregnancy		
97	28	None	Pregnancy	Decidua	1 mo.
98	33	Placenta previa	Pregnancy	Decidua	5 mo.
99	36	None	Pregnancy	Decidua	6 mo.
100	39	Chorioepithelioma	None	Proliferative	3 mo.

endometriums had responded to the stimulation received from the respective corpora lutea. Ovulation had occurred and corpus luteum development had progressed normally in these individuals during a prolonged phase of active endometrial bleeding. The findings in Patient 89 were similar to the two just described, except that the corpus luteum was cystic (Table I). The individual cells appeared normal. The endometrium evidenced progravid changes which indicated that the corpus luteum had exerted its influence in spite of its cystic condition. Ovulation undoubtedly had occurred during the active bleeding phase of six weeks' duration.

No endometrial cystic glandular hyperplasia was present in these patients who possessed corpora lutea and who complained of abnormal uterine bleeding.

One patient (Patient 92, Table I) complained of an oligomenorrhea. The endometrium was proliferative, and there was no corpus luteum in the ovaries when the tissues were removed on the eighteenth day.

Four patients complained of amenorrhea (Patients 93, 94, 95, and 96, Table I). One was in the menopause (Patient 95) and another was eleven years postmenopausal (Patient 96). Patient 94 was operated upon on the thirty-ninth day of the cycle. At this time the menstrual period was thirteen days overdue. She had never missed a period before. A normal corpus luteum in the vascularization stage was present in the ovary. The endometrium was early progravid. These findings would be expected about the thirteenth day of this patient's usual twenty-six-day cycle. The evidence indicates that a complete cycle had passed without a bleeding phase and that ovulation of the next cycle had occurred in a perfectly rhythmic manner. Markee (1940) has observed similar cyclic manifestations of ovulation in the monkey *(Macacus rhesus)*.

Three patients (Patients 97, 98, and 99) were pregnant when the uterus was removed (Table I). The endometriums had the normal decidua, glands, and vascular development of pregnancy. The corpora lutea were normal.

One patient (Patient 100, Table I) had a chorioepithelioma and had been bleeding continuously for three months. No corpus luteum was demonstrable in either ovary. The endometrium was proliferative in type.

SUMMARY

Ovulation had occurred in these 100 unselected and consecutively operated patients in a manner similar to that observed in normal women. Forty-six patients had functioning corpora lutea of the present cycle. Not counted in the 46 patients were many patients who are listed as not having corpora lutea of the present cycle but who had corpora lutea of the previous cycle in the regression phase. Their presence suggests that ovulation, corpus luteum development, and the

endometrial response had occurred normally in the preceding cycle. The findings indicate that ovulation takes place most frequently about the midpoint of the menstrual cycle as in normal women. In one instance, ovulation occurred on or about the sixth day (Patient 76). Ovulation occurred early in the cycle also in Patient 77. Ovulation occurred after a period of amenorrhea in one patient (Patient 94). This is identical to the phenomenon as it is observed in normal women without fibroids. Four of these 100 patients were pregnant or had a complication of pregnancy at the time of operation. This indicates positively that ovarian function can be normal in women with fibroids.

There were two corpora lutea with identical development in the ovaries of each of 4 patients. In another patient, there were two corpora lutea in one ovary and one in the other ovary, all having the same degree of development. Multiple ovulation occurs in normal women in approximately the same number of instances as found in these 100 patients.

Ovulation in three instances occurred during a prolonged phase of active uterine bleeding (Patients 87, 89, and 90).

In the 37 patients with normal menstrual cycles (Figs. 1 and 2), ovulation had failed to occur by the fifteenth day in but one patient. This patient (Patient 8) demonstrated, in all probability, an instance of cyclic anovulatory menstruation which is not strictly an abnormal phenomenon.

In all the patients complaining of abnormal uterine bleeding (Figs. 3, 4, and 5), ovulation had not occurred by the fifteenth day in 14 patients but had occurred in 21 patients.

Four additional patients were menopausal or postmenopausal. In these ovulation, as would be expected, had not occurred.

If 100 normal women were operated upon consecutively without consideration of the stage of the cycle, it is doubtful if ovulation would be found with any greater frequency than was observed in the patients studied in this report.

The development of the corpora lutea was normal in 41 of the 46 patients. Evidence that the development was normal was obtained by histologic study of the corpora lutea and by the histologic study of the endometriums which reflected the characteristic responses to normal corpus luteum hormonal stimulation. In those patients with abnormal uterine bleeding, the normal relationship between the corpus luteum and the endometrium was maintained in most instances.

Small follicular cysts were present in 21 of the 100 patients. In no instance was there evidence that these cysts had had any influence on the normal physiologic processes of the ovaries or the endometriums. Normal functioning corpora lutea were present in the ovaries of 5 of these patients. Hyperplasia or excessive estrogen stimulation of the endometrium was present in none.

So-called cystic glandular hyperplasia was present in a moderate degree in only one instance in the entire group of 100 patients with fibroids. This finding is at marked variance with the generally accepted clinical impression.

CONCLUSIONS

All of the above facts obtained from a critical study of these 100 patients with uterine fibroids indicate that the ovarian and endometrial relationships were not significantly altered in the cycles observed. There was no evidence of excessive or unopposed estrogenic stimulation.

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104 SOUTH MICHIGAN BOULEVARD

DISCUSSION

DR. GEORGE H. GARDNER.—No one doubts that women with fibroids ovulate normally at times, but it is amazing that "functioning" corpora lutea were found in 47 per cent of this unselected series. Uterine fibroids are at times accompanied by enlarged, gray, edematous, cystic ovaries. Consequently, it is disconcerting that these so-called "oyster ovaries" were almost absent from the Brewer-Jones series. Two of their other observations are strong evidence against the improbable thesis that uterine fibroids result from prolonged, excessive, estrogenic hormone stimulation, for hyperplasia of the endometrium was encountered only once, and corpora lutea with corresponding secretory response by the endometriums were frequent, not exceptional, findings.

Certain "misfit" cases, i.e., those in which the response of the endometrium did not coincide with the appearance of the corpus luteum, have been presented. I believe that the authors are justified in using this term and in presuming to estimate corpus luteum function, from the histologic appearance of lutein cells.

These cases conclusively demonstrate that functional uterine bleeding may arise from secretory endometrium and that bleeding is not invariably anovulatory. Some of the misfits are striking examples, both of irregular ripening and irregular shedding of the endometrium. Such observations are additional proof that the uterine mucosa does not always follow the rule of "all or none" response to hormone stimulation. Local mechanical interference by the uterine fibroids suggests itself as an explanation for the presence of some "misfit" cases. Tumors may compress, distort and so interfere with the blood supply of the ovaries that their function is seriously altered; as a result both follicles and corpora lutea may mature slowly and unequally; by the same token, the corpora lutea may involute in an unusual manner. In consequence the progesterone stimulation of the endometrium may lack rhythm, be protracted, and even be modified by the developing follicle of an oncoming cycle. Furthermore, the structure of the endometrium may be so disturbed by fibroids, especially those which encroach on the uterine cavity, that it cannot respond in its usual

manner even to normal hormone stimulation. Spiral arteries may be inadequate or abortive; this might lead to premature focal ischemia of the mucosa and result in abnormal uterine bleeding.

DR. RALPH A. REIS.—When someone as capable as Dr. Brewer denies his ability to handle more than 100 cases it takes courage to speak on 1,000. We analyzed 1,000 cases at Michael Reese Hospital. First, we found no relation between the state of the endometrium and the state of the cyclic development of the corpus luteum and other changes. Second, the bleeding that occurred as we found it was either on a mechanical basis due to submucous fibroids or from pressure atrophy of the endometrium, or from a rather frequent association of adenomyosis and fibroids. It is our impression that in many of our patients the bleeding is not due to intramural or submucous fibroids but to adenomyosis and fibroids. In our 1,000 cases there were about 25 per cent that showed ovarian pathology. I think that refutes Witherspoon's theory that chronic inflammation sets up a cycle that eventuates fibroids.

I would like to ask Dr. Brewer whether in these 100 patients adenomyosis of the uterine wall was found to any extent.

DR. BREWER (closing).—In answer to Dr. Reis' question, there were not more than five that had adenomyosis associated with fibroids. There were many more patients with endometriosis.

AN ANALYSIS OF SOME FACTORS ASSOCIATED WITH POSTTOXEMIC HYPERTENSION

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AS EARLY as 1851, Frerichs[1] thought that eclampsia might cause a subsequent "chronic nephritis." The earlier literature, summarized by Koblanck[2] (1894), was based chiefly upon autopsy findings, or upon the detection of proteinuria at follow-up. Later studies have included blood pressure measurements, and the demonstration of hypertension at follow-up has been taken as evidence for chronic nephritis, even long after the establishment of the conception of vascular hypertension. After reviewing the literature most capably, Bell[3] (1932) concluded that a mild degree of change in the renal blood vessels may often persist after toxemia of pregnancy. He believes that the later hypertension found by so many writers may be caused by the persistence of the glomerular capillary changes which he had found in his own material. Other recent reviews of the literature of posttoxemic hypertension have been given by Siedentopf and Major[4] (1936) and Browne and Dodds[5] (1939).

The estimated frequency of hypertension in such follow-up studies ranges from less than 2 per cent to over 60 per cent. The average incidence of hypertension after toxemia of pregnancy would seem to be about 45 per cent, to judge from the literature.

Henceforth, follow-up studies will be more comparable among themselves, and many cases from different clinics can be "pooled" in the literature. We are indebted to the American Committee on Maternal Welfare for a uniform terminology and set of criteria for the classification of the toxemias.

In the present paper we shall report the findings at follow-up in a large series of nonconvulsive toxemias classified by the new system. Vomiting of pregnancy has been excluded. An analysis of factors associated with later hypertension will be presented.

MATERIAL AND METHODS

In 1935 and 1936 the 10,627 deliveries in the Margaret Hague Maternity Hospital included 645 cases of late nonconvulsive toxemia, an incidence of 6.07 per cent. In 1940 we have re-examined 466, or 72 per cent, of these toxemias.

Blood pressure readings were made with a mercury sphygmomanometer, with the patient lying down. After a rest period of five minutes, and quiet reassurance, the pressure was checked. The lower reading is reported. The diastolic pressure was taken as the point at which the sounds suddenly became muffled and dull. The eye grounds were examined without mydriasis. The cardiac size was estimated by palpation of the point of maximal impulse; when this was not felt, 6 foot x-ray plates were taken. When the specific gravity of the morning urine was less than 1.022, blood chemistries and urea clearances were done.

Urinary protein was determined by the sulfosalicylic acid method. Blood and urine ureas were measured by Van Slyke's[6] manometric procedures. Usually the urine output permitted the calculation of maximal clearances; voided urines were used, and the patients were ambulatory.

The new toxemia classification adopted by the American Committee on Maternal Welfare[7] was used to classify the patients upon the basis of the information available at the time of the toxic pregnancy of 1935 or 1936, and without regard for the status at follow-up. When the toxemic manifestations (hypertension, proteinuria, edema) were definitely known to have first appeared later than the twenty-fourth week of pregnancy, the toxemia was called *pre-eclampsia. Mild* and *severe* pre-eclampsia were divided on the basis of blood pressure below or above 160/110,

TABLE I. DISTRIBUTION OF THE TOXEMIAS RE-EXAMINED IN 1940

All patients had toxemia in 1935 or 1936. "Hypertension" refers to any blood pressure greater than 140/90. All percentages based upon numbers of patients seen in 1940.

GROUP	NUMBER OF CASES	IMMEDIATE DEATHS	REMOTE DEATHS	FETAL MORTALITY PER CENT	FOLLOW-UP FINDINGS				PREGNANT AGAIN	RECURRENCE OF TOXEMIA PER CENT
					HYPERTENSION PER CENT		PROTEINURIA PER CENT			
Mild pre-eclampsia	267	0	5	7.12	37.45	(32.60)*	21.0	(2.3)†	134	32.8
Severe pre-eclampsia	52	3	1	38.50	42.32	(36.55)	17.3	(1.9)	21	66.7
Renal disease	14	0	4	57.14	78.60	(78.60)	78.6	(78.6)	0	
Hypertension	41	0	3	34.15	100.00	(100.0)	41.5	(2.4)	9	88.9
Hypertension (?)	41	0	2	29.27	87.80	(87.80)	28.2	(2.6)	19	73.7
Unclassified	51	0	1	27.45	72.58	(51.00)	33.3	(10.0)	20	65.0
Total	466	3	16	19.85	53.08	(47.22)	26.2	(5.5)	203	45.8

*Figures in parentheses exclude patients with either systolic or diastolic elevation alone.

†Figures in parentheses exclude patients showing only a "very faint trace" of protein by sulfosalicylic acid method.

proteinuria less or more than 6 Gm. per liter, edema slight or marked, the absence or presence of symptoms, and the response to treatment. When known hypertension antedated the pregnancy, or appeared before the twenty-fourth week, it was considered that the patient had either *hypertensive* or *renal disease.* These were differentiated on the basis of history, degree of proteinuria, type of urinary sediment, and renal function tests. The *unclassified toxemias* are those in which the data were incomplete. As a subgroup of the *unclassified* category we have separated patients thought to belong with the hypertensives, because of the absence of all signs and symptoms other than a blood pressure greater than 180/100. However, their status before the twenty-fourth week of pregnancy was unknown, so we have called them *"hypertension (?)."* Since 88 per cent of these had hypertension at follow-up, it seems that this criterion has some value. The distribution of the different groups is set forth in Table I. Only those patients seen in 1940 are included in any of the tables and analyses to be presented.

Our standard for hypertension is any pressure greater than 140 mm. Hg in the systolic or 90 mm. Hg in the diastolic readings.

REMOTE MATERNAL MORTALITY

Of the 642 survivors discharged from the hospital, 16, or 2.96 per cent, are known to have died; 12 of these deaths were in the cardiovascular field, 4 being associated with toxemia in the subsequent pregnancy. Table I shows the distribution of these remote deaths in relation to the toxemia classification.

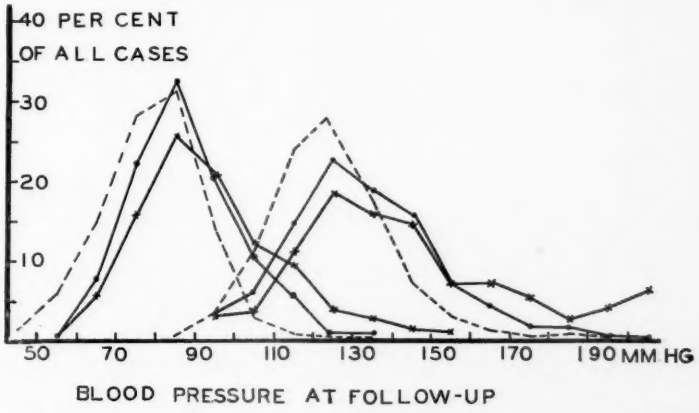

Fig. 1.—The frequency distributions of diastolic and systolic blood pressures at follow-up in 1940, as compared with control series described in text. Control series from publications of Alvarez and Zimmermann, Wetherby, and Saller. Patients who had mild pre-eclampsia in 1935 or 1936. All patients having nonconvulsive toxemia in 1935 or 1936. Controls, ------; mild pre-eclampsia, .—.—.; all cases, x—x—x.

FINDINGS AT FOLLOW-UP

Hypertension.—Table I shows that very nearly half (47.2 per cent) of all nonconvulsive patients re-examined now have hypertension at 3½ to 5½ years after the toxemia of 1935 or 1936. A few patients have an elevation in either the systolic or the diastolic pressure, but not in both. If these be considered as hypertensive, then the incidence of hypertension becomes 53.08 per cent. In Fig. 1 are plotted the frequency distributions of the systolic and diastolic pressures as found at follow-up.

We have used, as a control series, the published data of 3 writers who have described the range of blood pressure in women. Wetherby[9] reports the pressures in women attending the outpatient clinic in Minneapolis. Of this series, 1,544 cases are in the age groups represented by our patients. A second series is that of Alvarez and Zimmermann[10] for 216 unmarried women from the office practice of Alvarez in

California. The third is that of Saller[11] from the Kiel outpatient clinic; of these, 1,142 are in the same age groups as our patients. The age groups of these control series were weighted so as to correspond with the age distribution in our posttoxemic women, and the data of the 3 series were combined. The corrected frequency curves were then drawn in Fig. 1, which also compares the blood pressures found in our posttoxemic patients.

As one compares the control curves with those for the posttoxemic women, it is evident that there is a greater incidence of hypertension in the posttoxemics, whatever blood pressure level one may choose as the dividing line between normal and hypertensive states.

Proteinuria.—In 73.8 per cent of all patients, no protein was detected in the voided urine at follow-up. In the great majority of the rest, the proteinuria was only a "very faint trace" by the sulfosalicylic acid method. Short and Ley[12] have recently demonstrated as much protein in the urines of 20 to 30 per cent of nearly 5,000 women life insurance policy holders. In 5.5 per cent of all our cases, the proteinuria was present in possibly significant degree. Most of these patients were in the renal disease or unclassified groups. Table I presents the results for each category of toxemia.

Blood Chemistry.—The only blood chemical findings of any significance were in the renal disease group, and in 12 patients who now have recognizable diabetes. In 10 of these diabetics, the hyperglycemia has appeared since the toxic pregnancy of 1935 or 1936.

Urea Clearance.—Urea clearances were not done in 229 of the cases, since the urinary specific gravity exceeded 1.022 in the absence of proteinuria and sugar, and

TABLE II. RENAL FUNCTION AT FOLLOW-UP

	URINARY SPECIFIC GRAVITY MORE THAN 1.022	URINARY SPECIFIC GRAVITY LESS THAN 1.022				TOTAL WITH RENAL IMPAIRMENT PER CENT
		NORMAL BLOOD PRESSURE		HYPERTENSION		
		UREA CLEARANCE LESS THAN 60 PER CENT	UREA CLEARANCE MORE THAN 60 PER CENT	UREA CLEARANCE LESS THAN 60 PER CENT	UREA CLEARANCE MORE THAN 60 PER CENT	
Mild pre-eclampsia	161	1	56	5	44	2.25
Severe pre-eclampsia	19	1	15	3	14	7.69
Renal disease	0	2	0	10	2	85.70
Hypertension	12	0	0	2	27	4.88
Hypertension (?)	14	0	1	3	23	7.32
Unclassified	23	3	3	2	20	9.81
Total	229	7	75	25	130	6.87

TABLE III. ANATOMIC FINDINGS IN PATIENTS HYPERTENSIVE AT FOLLOW-UP

GROUP	EYE GROUND CHANGES			CARDIAC ENLARGEMENT			RADIAL ARTERY SCLEROSIS CASES
	CASES	PER CENT OF ALL CASES	PER CENT OF HYPERTENSIVES	CASES	PER CENT OF ALL CASES	PER CENT OF HYPERTENSIVES	
Mild pre-eclampsia	30	11.36	30.30	29	10.97	29.30	0
Severe pre-eclampsia	11	21.15	50.00	9	17.32	40.90	1
Renal disease	8	57.20	72.70	8	57.20	72.70	0
Hypertension	23	56.10	56.10	26	63.40	63.40	7
Hypertension (?)	21	51.20	58.35	21	51.20	58.35	2
Unclassified	16	31.38	43.25	12	23.53	32.42	2
Total	109	23.45	44.30	105	22.58	42.68	12

it was thought that the clearances would be normal (Chesley[13]). Of the remaining 237, only 32 had urea clearances below 60 per cent (taken as the lower limit of normal). Twelve of these were in the renal disease group. At most, then, only 6.9 per cent of the posttoxemics show renal impairment. Excluding the cases of renal disease, only 4.3 per cent have demonstrably impaired kidney function. The results for the different groups are summarized in Table II.

Physical Findings.—Of the 246 patients found to have hypertension at follow-up, 109 (44.3 per cent) had eye ground changes, and 105 (42.7 per cent) had cardiac enlargement. In addition to these hypertensives, 6 women with normal blood pressures show eye ground changes, and 1 has cardiac enlargement (rheumatic heart disease). The results of the physical examinations are detailed in Table III.

FACTORS AFFECTING THE PERSISTENCE OF HYPERTENSION AND THE RECURRENCE OF TOXEMIA

In the analysis of factors affecting the persistence of hypertension, the pre-eclamptic group patients (319) provide the data unless otherwise specified. For recurrence of toxemia, the data are for the 145 pre-eclamptic patients having subsequent pregnancies.

In general, the same factors affect the recurrence of toxemia as affect the persistence of hypertension. While many of these factors are of purely academic interest when considered in relation to permanent hypertension alone, they have a very definite practical value in their relation to the recurrence of toxemia. As will be demonstrated, another toxic pregnancy, after a first toxemia, increases the chances of later hypertension. If one can judge the probabilities of recurrence of toxemia, perhaps some degree of control over the later appearance of hypertension may be expected.

Family History.—We do not consider that the family histories possess any high degree of reliability, but nevertheless there does appear to be a correlation between hypertension at follow-up and the patients' stories of high blood pressure, "heart trouble" (nature unspecified), kidney trouble, strokes, and diabetes in near relatives. We have combined these various manifestations of possible cardiovascular disease; whenever such a positive history was elicited in the pre-eclamptic groups, the chances for hypertension were increased. The effect upon the recurrence rate for toxemia is slight (Table IV).

TABLE IV.—THE EFFECT OF FAMILY HISTORY OF CARDIOVASCULAR DISEASE IN ENHANCING THE PROBABILITY OF HYPERTENSION AND RECURRENCE OF TOXEMIA

	FAMILY HISTORY NEGATIVE	FAMILY HISTORY POSITIVE
Incidence of hypertension at follow-up	21.2%	36.1%
Recurrence rate of toxemia	37.7%	48.1%

TABLE V. THE RELATION BETWEEN THE FIRST OBSERVED SYSTOLIC BLOOD PRESSURE, BEFORE ONSET OF TOXEMIA, AND THE INCIDENCE OF LATER HYPERTENSION AND RECURRENCE OF TOXEMIA

INITIAL BLOOD PRESSURE	LESS THAN 100	101-110	111-120	121-130	131-140	141 PLUS
Incidence of hypertension at follow-up	7.69%	20.51%	35.90%	55.20%	43.23%	46.67%
Recurrence of toxemia	0.0 %	20.0 %	40.6 %	51.5 %	41.7 %	42.1 %

Initial Blood Pressure Reading.—The lower the first observed systolic blood pressure, one month or more before delivery, the less likely toxemia is to recur, or hypertension is to be found at follow-up. This is true especially in the normal, and even the low normal range of blood pressure. Taking only the pre-eclamptic patients (though the same observation is valid for all cases), we find the conditions as indicated in Table V.

The first observed systolic pressure is often higher than subsequent readings, before the onset of toxemia. Perhaps the patients with the higher initial pressures have reacted more to the emotional stimulus of the first clinic visit. This interesting correlation between the first observed blood pressure and subsequent hypertension might be compared with the predictive value of the cold pressor test for hypertension as alleged by Hines and Brown.[14] Robinson and Brucer[15] examined a large number of life insurance policy holders at yearly intervals, and found that "... men with moderately high systolic pressures (120 to 140 mm.) at any age, but especially in the younger groups, are probably the ones who will have hypertension years later."

Time of Onset and Duration of Toxemia.—Since patients having an early onset of toxemia are liable to be carried for prolonged periods, to improve the chance of fetal survival when delivered, the time of onset and duration of toxemia will be considered together. In addition, however, we shall attempt to separate these factors in their influence upon permanent hypertension and upon the recurrence of toxemia.

Onset of toxemia before the thirty-eighth week is associated with a greater probability of toxemia recurrence and of hypertension at follow-up, though there is apparently no direct relation between time of onset and these sequelae (Table VI).

TABLE VI. THE INCIDENCE OF LATER HYPERTENSION AND RECURRENCE OF TOXEMIA AS INFLUENCED BY TIME OF ONSET OF TOXEMIA

ONSET OF TOXEMIA	BEFORE SEVENTH MONTH	SEVENTH TO EIGHTH MONTH	EIGHTH TO EIGHT AND ONE-HALF MONTH	EIGHT AND ONE-HALF TO NINTH MONTH	POST-MATURELY
Incidence of hypertension at follow-up	62.5%	40.0%	53.2%	15.8%	26.5%
Recurrence of toxemia	75.0%	42.8%	46.7%	26.8%	40.0%

TABLE VII. THE PARALLELISM OF DURATION OF TOXEMIA WITH THE INCIDENCE OF HYPERTENSION AT FOLLOW-UP AND WITH RECURRENCE OF TOXEMIA

DURATION OF TOXEMIA	0 TO 1 WEEK	1 TO 2 WEEKS	2 TO 3 WEEKS	3 TO 4 WEEKS	4 TO 6 WEEKS	MORE THAN 6 WEEKS
Incidence of hypertension at follow-up	13.7%	40.0%	48.6%	71.1%	66.7%	71.4%
Recurrence of toxemia	24.4%	29.0%	37.5%	72.2%	66.7%	100.0%

Considering the duration of toxemia without regard for the time of onset, we find the incidence of hypertension and recurrence of toxemia as shown in Table VII.

It appears that the duration of toxemia has a more nearly proportional effect upon subsequent hypertension and recurrence of toxemia than has the time of onset. In Fig. 2 we have plotted the data for mild and severe pre-eclamptics plus 97 eclamptics. Duration of toxemia parallels the incidence of later hypertension in all of these groups. However, these data have not been controlled with respect to time of onset of toxemia. Such an analysis is presented in Table VIII, which indicates strongly that time of onset of toxemia, per se, has no effect upon the appearance of hyperpiesia at follow-up. *The controlling factor is duration of toxemia.* This is true in women who have had no other toxemic pregnancy, as well as in women with history of an earlier or later toxemia. The recurrence of toxemia

TABLE VIII. THE EFFECT OF DURATION OF TOXEMIA, INDEPENDENTLY OF TIME OF ONSET, UPON THE INCIDENCE OF SUBSEQUENT HYPERTENSION, AND RECURRENCE OF TOXEMIA. DATA FOR MILD AND SEVERE PRE-ECLAMPTICS COMBINED

ONSET OF TOXEMIA CARRIED WITH TOXEMIA	BEFORE SEVENTH MONTH				SEVENTH TO EIGHTH MONTH				EIGHTH TO NINTH MONTH				POSTMATURE			
	MORE THAN 3 WEEKS		LESS THAN 3 WEEKS		MORE THAN 3 WEEKS		LESS THAN 3 WEEKS		MORE THAN 3 WEEKS		LESS THAN 3 WEEKS		MORE THAN 3 WEEKS		LESS THAN 3 WEEKS	
	CASES	PER CENT HYPERTENSION	CASES	PER CENT HYPERTENSION	CASES	PER CENT HYPERTENSION	CASES	PER CENT HYPERTENSION	CASES	PER CENT HYPERTENSION	CASES	PER CENT HYPERTENSION	CASES	PER CENT HYPERTENSION	CASES	PER CENT HYPERTENSION
Primiparas, and multiparas with no history of toxemia	6	66.7	4	0.0	5	60.0	10	10.0	19	63.2	85	15.3	1	100.0	20	15.0
Multiparas with history of toxemia, or history unknown	1	100.0	2	0.0	13	61.6	7	28.6	28	82.2	29	24.1	1	100.0	12	33.3
Eclampsia (series in preparation)	11	63.6	7	28.6	5	80.0	10	20.0	8	25.0	58	15.5	0	—	2	0.0
Total	18	66.7	13	15.4	23	65.3	27	18.5	55	67.2	172	16.8	2	100.0	34	20.6
Recurrence of toxemia in later pregnancies	5	60.0	6	33.3	10	70.0	20	35.0	24	62.5	97	33.3	1	100.0	27	25.9

also seems to depend upon the duration of the original toxemia. The data in Table VIII include the 97 eclamptic cases, added to augment the numbers of cases in each subdivision.

Height of Blood Pressure and Degree of Proteinuria in Toxemia.—The more severe the degree of hypertension during the toxic pregnancy, the greater the incidence of later hypertension and of toxemia recurrence. The same unfavorable prognosis holds when proteinuria increases concomitantly with hypertension. But this is not the most significant feature of the proteinuria. For at a given level of hypertension, the greater the proteinuria, the better the patient's chance of escaping hypertension at follow-up. Abundant proteinuria seems usually to augur well for the patient's future, as has been pointed out by Berman.[16] The data for pre-eclamptic patients are shown in Table IX.

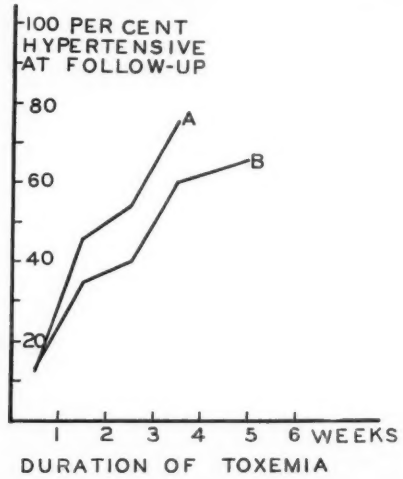

Fig. 2.—The relation between duration of toxemia in pregnancy and the incidence of hypertension at follow-up in 1940. *A*, Patients who had mild pre-eclampsia in 1935 or 1936. *B*, Patients who had mild or severe pre-eclampsia in 1935 or 1936, together with all cases of eclampsia from 1931 to 1940.

Findings at Ten Days and Six Weeks Post Partum.—So far as the pre-eclamptics are concerned, neither the blood pressure nor the proteinuria at ten days has any significance in predicting subsequent hypertension. There is a marked relation between these findings and the recurrence of toxemia, which is nearly doubled in those patients whose toxic signs persist for ten days post partum. The blood pressure at six weeks post partum is a valuable indication as to the probability of toxemia recurrence or later hypertension, though it is not reliable by itself. In the summary in Table X, "elevated blood pressure" refers to any tension of 140/90 or greater.

Age at Follow-Up.—The older the patient at follow-up, the more likely hypertension is to be found. This is to be expected from the fact that the incidence of

TABLE IX. THE INCREASING INCIDENCE OF LATER HYPERTENSION AND RECURRENCE OF TOXEMIA IN RELATION TO INCREASING SEVERITY OF TOXEMIA

BLOOD PRESSURE AVERAGE, MM. HG	LESS THAN 140		141 TO 180		181 TO 220		MORE THAN 221	
PROTEINURIA, MORE OR LESS THAN 3 g/L	LESS	MORE	LESS	MORE	LESS	MORE	LESS	MORE
Incidence of hypertension at follow-up	37.5%	0.0	44.3%	21.0%	80.0%	53.8%	—	100%
Recurrence of toxemia	33.3%	0.0	41.5%	28.0%	—	66.7%		

hypertension rises with age in the population as a whole. Whether the *age when toxic* has an effect we can not say, since the follow-up period is nearly the same for all patients. The data for preeclamptics are shown in Table XI.

TABLE X. BLOOD PRESSURE AND PROTEINURIA IN THE PUERPERIUM AS RELATED TO THE REMOTE PROGNOSIS

STATUS IN PUERPERIUM	RECURRENCE OF TOXEMIA		STATUS AT FOLLOW-UP	
	CASES	PER CENT TOXIC	CASES	PER CENT HYPERTENSIVE
Blood pressure normal at 10 days	103	26.22	204	36.77
Blood pressure elevated at 10 days	43	60.50	101	39.60
Proteinuria less than 2 g/L at 10 days	134	34.35	286	38.12
Proteinuria more than 2 g/L at 10 days	8	50.00	22	31.81
Blood pressure normal at 6 weeks	79	26.58	150	27.33
Blood pressure elevated at 6 weeks	15	73.32	43	62.80

TABLE XI. AGE AT FOLLOW-UP IN RELATION TO THE INCIDENCE OF HYPERTENSION AND TO THE RECURRENCE OF TOXEMIA

	AGE AT FOLLOW-UP					
	BELOW 25	26 TO 30	31 TO 35	36 TO 40	41 TO 45	46 PLUS
Incidence of hypertension at follow-up	25.0%	26.7%	38.1%	53.6%	61.3%	77.8%
Recurrence of toxemia	15.7%	51.2%	54.5%	61.1%	71.4%	50.0%

Weight/Height Ratio at Follow-Up.—The greater the body weight relative to the height, the greater the incidence of high blood pressure at follow-up, and the greater the likelihood of toxemia recurrence. The increase is regular in all of the classes of toxemia. The data for pre-eclamptic patients are given in Table XII. Possibly weight control in patients who have had toxemia of pregnancy would reduce the incidence of subsequent hyperpiesia.

TABLE XII. THE EFFECT OF THE WEIGHT/HEIGHT RATIO UPON THE INCIDENCE OF HYPERTENSION AT FOLLOW-UP AND UPON THE RECURRENCE OF TOXEMIA

WEIGHT / HEIGHT, LB./INCH	LESS THAN 1.80	1.81 TO 2.00	2.01 TO 2.20	2.21 TO 2.40	2.41 TO 2.60	2.61 TO 2.80	MORE THAN 2.81
Incidence of hypertension at follow-up	15.4%	15.9%	22.4%	40.0%	60.0%	53.9%	62.7%
Recurrence of toxemia	45.5%	30.4%	12.5%	33.3%	50.0%	60.0%	68.2%

Subsequent Pregnancies.—Perhaps one of the most important practical considerations is what advice to give a patient with toxemia, concerning future pregnancies. In our patients, subsequent *normal* pregnancies are associated with a low incidence of hypertension at follow-up. But another toxemia will increase the probability of later high blood pressure. In the pre-eclamptic patients we found the data as shown in Table XIII.

Since many of our pre-eclampsia patients had had pregnancies previous to the toxic gestation of 1935 or 1936, we have made a further analysis of the effect of other pregnancies and toxemias upon the remote prognosis. Here again it is evident that the chances for appearance of future hypertension are augmented by a second toxemia. The data for pre-eclamptic patients are shown in Table XIV.

TABLE XIII. THE NATURE OF SUBSEQUENT PREGNANCIES AND THE INCIDENCE OF LATER HYPERTENSION

SUBSEQUENT PREGNANCY	NONE	ONE		TWO		
		TOXIC	NORMAL	BOTH TOXIC	ONE TOXIC ONE NORMAL	BOTH NORMAL
Incidence of hypertension	44.7%	64.6%	11.7%	80.0%	50.0%	8.3%

TABLE XIV. THE INCIDENCE OF HYPERTENSION AS CORRELATED WITH THE NATURE OF ALL PREGNANCIES OTHER THAN THE TOXIC ONE OF 1935 OR 1936

ALL OTHER PREGNANCIES	NONE	ALL NORMAL	TOXEMIA IN AT LEAST 1 OTHER	HISTORY OF TOXEMIA UNCERTAIN
Incidence of hypertension at follow-up	31.5%	8.5%	61.9%	58.1%

The interval from delivery, in the toxic pregnancy, to the subsequent conception bears no definite relation to the incidence of later hypertension, or to the recurrence rate of toxemia (Table XV).

TABLE XV. THE INTERVAL FROM TOXEMIA TO SUBSEQUENT CONCEPTION IN ITS BEARING UPON THE INCIDENCE OF LATER HYPERTENSION AND THE RECURRENCE OF TOXEMIA

DELIVERY TO CONCEPTION	LESS THAN 3 MONTHS	3 TO 6 MONTHS	7 TO 12 MONTHS	13 TO 24 MONTHS	25 TO 36 MONTHS	MORE THAN 37 MONTHS
Incidence of hypertension at follow-up	33.3%	38.5%	39.2%	25.7%	38.1%	45.5%
Recurrence of toxemia	33.3%	35.7%	36.4%	34.2%	42.9%	54.6%

Ante-partum Care.—The recurrence rate of toxemia in later pregnancies was not reduced by the medical care given in these later pregnancies. The number of patients receiving no care is too few to form an accurate opinion, but it appears that the recurrence rate of toxemia was increased in those pre-eclamptic patients who placed themselves under medical supervision before delivery.

These data, while discouraging, in no way negate the desirability of prenatal care, in fact, they point to its value. Since so many patients once toxic will again have toxemia, prenatal care becomes of paramount importance, for the incidence of *severe* toxemia can undoubtedly be reduced. Also it should be emphasized that our data concern only the *recurrence* of toxemia. The data for all cases, including 116 eclamptic patients pregnant again, are set forth in Table XVI.

Fruitfulness of Later Pregnancies.—Among the 466 patients who have been re-examined recently, 200 have had 247 pregnancies since 1935 or 1936. Of these 247 pregnancies, 190 (76.9 per cent) were live births, 44 (17.8 per cent) were abortions, and 13 (5.3 per cent) were stillbirths. Of the 203 pregnancies carrying past the twenty-fourth week, 93 (45.8 per cent) were again toxic, 108 (53.2 per cent) were normal, and 2 were uncertain.

Four mothers (2 per cent) died in the subsequent pregnancy.

GENERAL DISCUSSION

Our analysis demonstrates that about half of all nonconvulsive toxemia patients have hypertension when re-examined three and one-half to five and one-half years after the toxemia, at a time when temporary eleva-

TABLE XVI. PRENATAL CARE AND THE RECURRENCE OF TOXEMIA IN LATER PREGNANCIES

	NO PRENATAL CARE		PRIVATE CARE		CLINIC PRENATAL CARE							
					LESS THAN 2 MONTHS		2 TO 3 MONTHS		3 TO 4 MONTHS		MORE THAN 4 MONTHS	
	CASES	PER CENT TOXIC	CASES	PER CENT TOXIC	CASES	PER CENT TOXIC	CASES	PER CENT TOXIC	CASES	PER CENT TOXIC	CASES	PER CENT TOXIC
Eclampsia	11	54.6	33	51.5	28	53.6	9	22.2	8	37.5	27	51.8
Mild pre-eclampsia	6	16.7	21	28.6	20	30.0	30	43.3	20	30.0	21	38.1
Severe pre-eclampsia	4	25.0	4	75.0	6	100.0	2	50.0	1	100.0	6	66.7
Renal disease	0		0		0		0		0		0	
Hypertension	0		3	100.0	3	66.7	4	75.0	1	100.0	2	50.0
Hypertension (?)	2	50.0	3	66.7	3	66.7	5	80.0	5	80.0	0	
Unclassified	1	100.0	5	60.0	3	33.3	6	66.7	1	100.0	3	100.0
Total	24	41.7	69	49.3	63	50.8	56	48.2	36	44.5	59	50.8
Eclampsia and pre-eclampsia	21	38.1	58	44.8	54	50.0	41	39.0	29	34.5	54	48.2

tions may be expected to have subsided and before advancing age has had a maximum effect.

Many factors are correlated in more or less significant degree with the incidence of hypertension as found at this time. These factors may be considered in three groups, according to our ability to influence them, and thus postpone (or possibly even prevent) later hypertension.

1. Factors beyond our control:
   a. Family history of cardiovascular renal disease.
   b. Initial blood pressure level ante partum.
   c. Age when toxic.
   d. Age at follow-up.
   e. Parity at time of toxemic pregnancy.
2. Factors which may possibly be modified:
   a. The severity of the toxemia, and therefore
   b. the status at ten days and six weeks post partum.
   c. The weight-height ratio at follow-up.
3. Factors which can be modified.
   a. Duration of the toxemia.
   b. Subsequent toxemia.

Fortunately these latter factors are those with a most profound effect on subsequent hypertension, and give opportunity for reduction of the incidence of high blood pressure in posttoxemic women.

Since the incidence of posttoxemic hypertension increases so markedly with the duration of the toxemia (Fig. 2), it would appear that the prompt delivery of the toxemic patient whose disease appears any time in the last trimester of pregnancy might reduce the incidence of hypertension by two-thirds, to about 13 per cent. Thus of the 121 women now hypertensive after pre-eclampsia, 80 could have been spared. The remote interests of the mothers are best served by interruption of the pregnancy, and the immediate fetal welfare is similarly improved by prompt delivery after thirty-five weeks. This consideration must be balanced against other factors which will vary from case to case. Induction of premature labor is not always easy, especially in the primigravidas in whom pre-eclampsia is most common. Operative interference always carries hazards of morbidity and even maternal mortality, as well as of some fetal loss. Since the policy of the Margaret Hague Maternity Hospital has been conservative, interruption of pregnancy has usually been reserved for the more severe cases of toxemia. Our statistics are not, therefore, suitable for analysis as an approach to the problem of balancing the immediate maternal interest against the remote maternal interests and the fetal interest.

The control of subsequent toxemia appears to lie wholly in advising against subsequent pregnancy in those patients with statistically great chance of subsequent toxemia, as present methods may only modify but not prevent toxemia.

FETAL MORTALITY

Since only the patients who were re-examined in 1940 have been included in the analyses, the fetal mortalities recorded here are not exact. Our chief concern is to determine those factors affecting the

mortality which also bear upon the incidence of future hypertension in the mother. These factors are severity and duration of the toxemia.

Fetal mortality increases with either the blood pressure or the proteinuria, or both together. Thus in severe pre-eclampsia, the fetal mortality is more than 5 times that in mild pre-eclampsia (Table I). In all groups of toxemia, except the mild pre-eclamptics, the higher blood pressures and proteinurias are associated with increased fetal loss.

The data bearing upon the duration of toxemia in relation to fetal mortality are derived from the pre-eclamptic groups. In these pre-eclamptic patients, fetal deaths mount with continuing toxemia. Often a patient may be carried along with toxemia, supposedly in the fetal interests, only to have the fetus die in utero. Our data may be summarized, combining mild and severe pre-eclamptics, as shown in Table XVII.

TABLE XVII. THE RISE IN FETAL MORTALITY WITH PROLONGATION OF TOXEMIA

DURATION OF TOXEMIA	LESS THAN 1 WEEK	1 TO 2 WEEKS	2 TO 4 WEEKS	MORE THAN 4 WEEKS
Fetal mortality	2.3%	10.6%	13.9%	20.7%

Thus, we see that the fetal interests coincide with the remote maternal interests, in that prolonged toxemia is deleterious to both.

SUMMARY AND CONCLUSIONS

We have re-examined, in 1940, 466, or 72 per cent, of all patients with nonconvulsive toxemias (exclusive of vomiting) who were admitted to the Margaret Hague Maternity Hospital in 1935 and 1936. The patients have been classified according to the new system recommended by the American Committee on Maternal Welfare.

The gross incidence of hypertension, greater than 140/90, at follow-up is 53 per cent. Among the hypertensives, about 45 per cent have eye ground changes and cardiac enlargement.

Proteinuria of possibly significant degree was found in 5.5 per cent of all cases.

Renal function at follow-up, as measured by urinary specific gravity and urea clearance tests, is normal in at least 93 per cent of the patients.

Since the toxic pregnancy of 1935 or 1936, diabetes has appeared in 10 patients; in 2 others diabetes was recognized at the time of the toxemia.

An analysis has been made of some of the factors associated with and possibly contributing to the finding of hypertension at follow-up.

The incidence of hypertension after pre-eclampsia, as found at follow-up, increases with:

1. Family history of cardiovascular disease.
2. Increasing blood pressure, even in the low normal range, as found at the first clinic visit.
3. Increasing age at time of toxemia (or at follow-up).
4. Earlier time in pregnancy of onset of toxemia (however, time of onset, per se, has *no* effect).

5. Longer duration of toxemia.
6. Greater severity of toxemia as judged by blood pressure.
7. Lesser severity of toxemia as judged by proteinuria.
8. Longer persistence of hypertension in days and weeks after delivery.
9. Increased ratio of weight to height, at follow-up.
10. Other toxic pregnancies.

The recurrence rate of toxemia in subsequent pregnancies is about 46 per cent. The factors affecting recurrence are the same as affect the incidence of later hypertension.

Fetal mortality increases with rising blood pressure, increasing proteinuria, and longer duration of maternal toxemia.

We wish to express our gratitude to Drs. S. A. Cosgrove, J. F. Norton, and E. G. Waters for their criticisms of the typescript. We are also indebted to many physicians who have permitted us to re-examine their private patients. Mrs. E. R. Chesley conducted the follow-up clinic. Most of the blood and urine urea determinations were made by Frances Orsato and Peter Marotta.

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Taeuber, C., and Taeuber, I. B.: German Fertility Trends, 1933-39, Am. J. Sociology **46:** 150, 1940.

As a result of 1,121,707 marriage loans made from August, 1933 to the end of 1938, enforcement of abortion laws, and several other interesting factors, the birth rate in the Reich had increased from 14.7 to 19.7. The effectiveness of control over abortion is shown in the decrease of abortions per 100 normal births from 103.4 in 1929 to 16.2 in 1936 and 18.1 in 1937.

The authors discuss the sociologic implications of marriage loans and similar devices for increasing the national fertility. A new divorce law is mentioned which has resulted in older men divorcing middle-aged wives and remarrying to rear second families. The German technique appears to be statistically more effective than the methods used in France and other European countries to obtain a deliberate increase in the birth rate.

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VITAMIN K ADMINISTERED TO THE MOTHER DURING LABOR AS A PROPHYLAXIS AGAINST HEMORRHAGE IN THE NEWBORN INFANT*

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THIS investigation has been conducted as two separate studies. Part I consisted of the determination of the prothrombin activity in normal newborn infants together with observations on the alterations in this activity which result from the administration of vitamin K to the mother. Part II was concerned with the practical application of the knowledge gained from the first study. It aimed to show the value of intra-partum vitamin K administration in reducing the incidence of hemorrhage in newborn infants.

LITERATURE

Dam,[1] in 1929, noted that chicks on a fat-free diet developed hemorrhagic disease. Later, Almquist[2] described the same tendency. In 1934, Dam and Schönheyder[3] were able to demonstrate that the antihemorrhagic factor necessary for the prevention of this disease was not to be found in any of the then known vitamins. However, they found that the unknown factor could be supplied by adding cereals and seeds common to the ordinary chick diet. Further work by Dam[4-6] revealed that green leafy plants, such as kale, alfalfa, and spinach were excellent sources of this antihemorrhagic factor and suggested the term "vitamin K" for this new food element. Subsequently, Schönheyder[7] proposed that the retardation of coagulation in vitamin K-deficient animals was due to hypoprothrombinemia.

Brinkhous, Smith and Warner[8] observed that otherwise normal newborn infants sometimes have relatively low prothrombin levels. In the same paper, they reported a case of hemorrhagic disease of the newborn in which the prothrombin value was less than 5 per cent of normal. Subsequent studies by this group[9] revealed that hypoprothrombinemia is physiologic from the second to the sixth day of life, i.e., during the period in which hemorrhagic disease of the newborn manifests itself. Hellman and Shettles[10] observed even lower levels of prothrombin in premature infants. This may help to account for the frequency with which intracranial hemorrhage complicates prematurity.

Waddell and Guerry,[11] in 1939, studied the effect of vitamin K on newborn infants. They administered vitamin K concentrate to alternate children in a series of twenty cases and observed that those who received the concentrate had a more rapid clotting time. They also reported "encouraging results" when this preparation was given in the antenatal period. In a preliminary report consisting of a relatively small number of observations, Hellman and Shettles[10] stated that "extremely low infant prothrombin levels can be raised by feeding vitamin K to the mother prior to delivery or directly to the infant after birth." Later, Shettles, Delfs and Hellman[12] reported that they were able to produce a normal adult prothrombin level in most newborn infants by feeding vitamin K concentrate to the mother during labor.

Although the chemical composition of vitamin K was not then known, Almquist,[13] in 1936, described a method for its isolation in concentrated form. Doisy and his

*Read at the New York Obstetrical Society, December 10, 1940.

associates[14] found the active principle of vitamin K to be a quinone. Shortly thereafter, four groups of investigators[15-18] announced the successful synthesis of several antihemorrhagic quinone derivatives. It is now generally agreed that 2-methyl-1, 4-napththoquinone is the most efficacious quinone derivative and that it is the most potent of the substances known to have vitamin K properties. Ansbacher, Fernholz and MacPhillamy[19] also noted that the natural vitamin is less rapidly absorbed by the animal organism than the synthetic compound. Waddell and Guerry[20] likewise found this substance to be as efficacious as vitamin K concentrate in the prevention of hemorrhagic disease of the newborn.

PART I

In the first part of this investigation, we determined the clotting activity in 200 newborn infants. The mothers of 100 of these were given 2 mg. of 2-methyl-1, 4-naphthoquinone (Thyloquinone)* by mouth, one-half to forty-four hours before delivery and a concurrent series of 100 cases in which the mother received no vitamin K therapy was used as a control group. Prothrombin activity estimations were made on each child in both series on the first, second, and fourth days of life. A total of 600 individual determinations, accordingly, were made. These observations demonstrate that vitamin K is of definite value in shortening the prothrombin clotting time in the newborn infant.

The "bedside" technique for estimating prothrombin activity as developed by Smith and his co-workers[21] was used in this part of our investigation. Although it produces consistently higher values than the more complicated two-stage method developed by the same group,[22] it was considered to be sufficiently accurate and to be more practical for clinical use in the newborn. The "bedside" test, like Quick's method[23] measures not only the amount of prothrombin present, but also its rate of convertibility to thrombin. Since both factors are important in the coagulation mechanism, this technique was preferred for our investigation.

The method is as follows: 0.1 c.c. of thromboplastin is placed in a 3 c.c. test tube. Blood, freshly drawn from the infant's external jugular vein, is added up to the 1 c.c. mark. The tube is inverted once and then tilted gently until clotting is complete, as evidenced by a failure of the blood to run down the tube in a changed position. The procedure is repeated on a normal adult as a control and the patient's clotting activity is expressed as a percentage of this normal:

$$\text{Clotting activity (in \% of normal)} = \frac{\text{Clotting time of control}}{\text{Clotting time of unknown}} \times 100$$

In our work, the thromboplastin was prepared by grinding 10 Gm. of ox or rabbit brain or lung and infusing it in 10 c.c. of normal saline solution for two hours. This was preserved in a refrigerator. Since the potency of thromboplastin diminishes with age, a control reading was taken every time the test was performed on a group of patients. If difficulty was encountered in withdrawing blood from the vein, the specimen was discarded and a fresh sample was drawn into a clean needle and syringe. Whenever the prothrombin clotting time of the control was appreciably under twenty-five seconds, the thromboplastin was diluted to bring the value up to this figure. In order to maintain a uniform standard, the same adult control (R. C.) was used throughout our study.

*Furnished through the courtesy of E. R. Squibb & Sons.

TABLE I. PROTHROMBIN ACTIVITY ON FIRST, SECOND, AND FOURTH DAYS OF LIFE (EXPRESSED AS A PERCENTAGE OF NORMAL ADULT PROTHROMBIN ACTIVITY). 100 CASES

PERCENTAGE OF NORMAL ADULT PROTHROMBIN ACTIVITY	A FIRST DAY NUMBER OF CASES	B SECOND DAY NUMBER OF CASES	C FOURTH DAY NUMBER OF CASES
10- 20	-	1	1
20- 30	-	6	4
30- 40	6 (20)	8 (48)	6 (26)
40- 50	7	14	7
50- 60	7	19	8
60- 70	21	18	17
70- 80	28	17	29
80- 90	16	8	15
90-100	9	6	8
100-110	4	3	4
110-120	2	-	1
Total	100	100	100
Mean	73.2% of normal	61.1% of normal	72.4% of normal

Variations in clotting activity (expressed as a percentage of adult normal clotting activity) observed on the first, second, and fourth days of life are shown in Table I. The values for the first day in 100 cases are given in the second column (A) and those for the second and fourth days are similarly tabulated in the third (B) and fourth (C) columns. On the second day, the clotting activity was less than 20 per cent of normal in one infant and from 20 to 30 per cent of normal in 6 other cases. Extremely low values persisted beyond the fourth day in 5 of these 7 infants. Of the 8 patients who had values of 35 per cent of normal or under, 4, or 50 per cent, showed evidence of hemorrhage; on the other hand, no bleeding occurred in any of the infants whose clotting activity was above this value. Although marked variations in prothrombin activity are shown by the values for each day, comparison of the figures in the three columns indicates, first, that normally the prothrombin activity diminishes rapidly on the second day and that this loss is, to some extent, regained by the fourth day. In other words, the number of infants showing clotting activity below 60 per cent of normal increased from 20 on the first day to 48 on the second and returned to 26 by the fourth day. Similar conclusions may be drawn from the mean values for each day. The mean clotting activity for the first day was 73.2 per cent of normal in the 100 cases. This fell to 61.1 per cent on the second day and returned to 72.4 per cent on the fourth day.

Table II illustrates the effect of vitamin K administered to the mother during parturition. The second column of this table represents the normal clotting activity values on the first day of life while the third column represents the values obtained in 100 infants whose mothers received vitamin K during labor. After the administration of vitamin K, only 3 infants showed clotting activity below 60 per cent of normal in contrast with 20 who did not have this prophylaxis.

The value of vitamin K as a means of increasing prothrombin activity in the newborn infant is still better shown in Table III. The figures in Column 2 show the control cases and those in Column 3 represent the infants of the mothers who received vitamin K during labor. In spite of the normal fall in prothrombin activity which occurs on the second day of life, only 8 infants who had received vitamin K had values for clotting activity below 60 per cent of normal while the control cases in this low field numbered 48. Since hemorrhage is most likely to occur in these infants with low prothrombin values, vitamin K used prophylactically reduced this risk in infants especially predisposed to bleeding to almost one-sixth of what it would have been without this prophylactic measure. The values in Column 3 so closely approach the normal adult values that we are justified in stating that vitamin K administered to the mother during labor prevents the customary drop in prothrombin activity which is seen soon after birth. The administration of vitamin

TABLE II. EFFECT OF VITAMIN K ON THE PROTHROMBIN ACTIVITY, FIRST DAY (EXPRESSED AS A PERCENTAGE OF NORMAL ADULT PROTHROMBIN ACTIVITY). 100 CASES

PERCENTAGE OF NORMAL ADULT PROTHROMBIN ACTIVITY	FIRST DAY OF LIFE	
	CONTROL CASES	VITAMIN K CASES
10- 20	-	-
20- 30	-	-
30- 40	6 } 20	- } 3
40- 50	7	1
50- 60	7	2
60- 70	21	4
70- 80	28	10
80- 90	16	20
90-100	9	27
100-110	4	27
110-120	2	3
120-130	-	4
130-140	-	2
Total	100	100
Mean	73.2% of normal	94.8% of normal

TABLE III. EFFECT OF VITAMIN K ON THE PROTHROMBIN ACTIVITY, SECOND DAY (EXPRESSED AS A PERCENTAGE OF NORMAL ADULT PROTHROMBIN ACTIVITY). 100 CASES

PERCENTAGE OF NORMAL ADULT PROTHROMBIN ACTIVITY	SECOND DAY OF LIFE	
	CONTROL CASES	VITAMIN K CASES
10- 20	1	-
20- 30	6	-
30- 40	8 } 48	- } 8
40- 50	14	3
50- 60	19	5
60- 70	18	3
70- 80	17	4
80- 90	8	33
90-100	6	25
100-110	3	20
110-120	-	5
120-130	-	1
130-140	-	1
Total	100	100
Mean	61.1% of normal	90.8% of normal

K to the mother accordingly causes the newborn infant's blood to clot as readily as that of a normal adult.

Table IV shows the values for the vitamin K cases and the controls on the fourth day of life. Here again there is a great reduction in the number of infants with low values after the use of vitamin K during labor. The lowest value obtained in any of the 100 cases was 38 per cent of normal, and all but 5 of the remaining 99 infants showed clotting activity equal to 50 per cent of normal or over during the first four days of life. None of the 100 vitamin K cases showed any evidence of hemorrhage. It would seem, therefore, that vitamin K eliminates the physiologic bleeding tendency at birth, by preventing the customary fall in prothrombin values on the second day, and by maintaining values which approach those of the normal adult during the early days of life when little or no vitamin K is available to the infant.

Comparison of the prothrombin values on the first, second, and fourth days with the results which followed the prophylactic administration of vitamin K to the moth-

ers, is facilitated by the graphs shown in Fig. 1. The three above the midline (A, B, C) represent the scatter of the control groups and those inverted below this line (D, E, F) show the distribution of the vitamin K cases. As might be expected in a series of this size, there is a wider scatter in all the graphs. However, a definite shift toward higher values in the vitamin K cases, as compared with the controls,

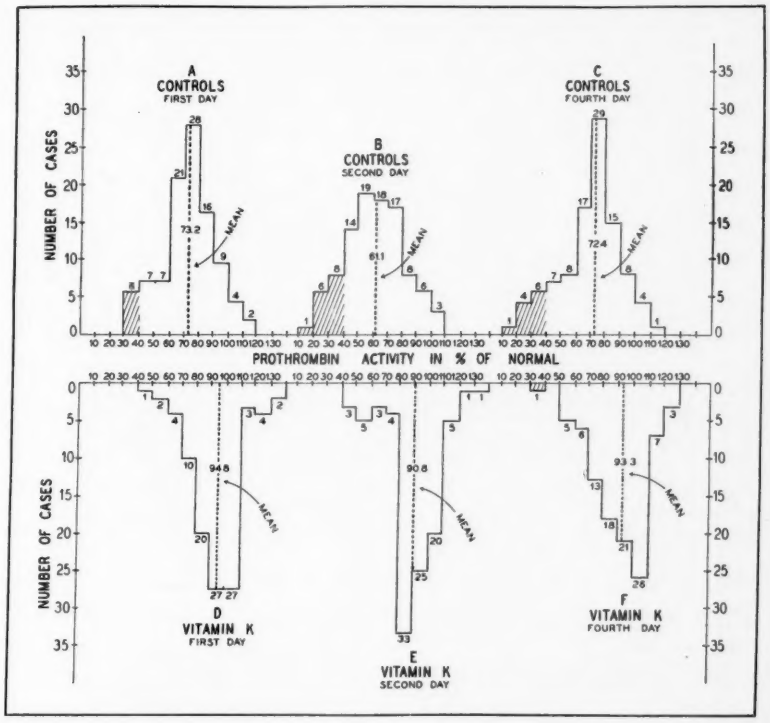

Fig. 1.—The upper three graphs represent clotting activity in 100 control cases on the first (*A*), second (*B*) and fourth (*C*) days. The number of cases are plotted perpendicularly while the horizontal figures show the percentage of normal clotting activity. The number of cases for each 10 per cent variation accordingly are blocked out in each of the three polygons. The mean percentage of normal clotting activity for each group is represented by the dotted line. The shaded areas indicate the clotting activities which fell below 40 per cent of the normal and were thus in the potential hemorrhage field. These three upper figures graphically show that the clotting activity is considerably diminished on the second day and tends to return toward normal by the fourth day of life.

The three inverted graphs represent the vitamin K cases on the first (*D*), second (*E*), and fourth (*F*) days. Aside from the fact that they are inverted, they are plotted in a manner similar to the upper graphs. They, therefore, show a definite shift to the right which illustrates the rather marked increase in prothrombin activity that results from the prophylactic use of vitamin K. In only one of the 300 observations (Graph F), did the clotting activity fall within the potential hemorrhage range, i.e., below 40 per cent of normal.

Comparison of the three inverted graphs also shows that the use of vitamin K tends to prevent the rather marked fall in prothrombin which normally occurs on the second day of life.

is evident. Not only do these higher values prevail but also the means of the 3 vitamin K graphs are nearly constant in contrast with the second day drop in the control group.

We have found no correlation between the prothrombin activity and sex, race, presence and degree of jaundice. One of our control cases developed erythroblastosis fetalis with icterus gravis. This infant's prothrombin activity was normal in each of the three observations. Four other controls who had prothrombin values of 17, 21,

TABLE IV. EFFECT OF VITAMIN K ON THE PROTHROMBIN ACTIVITY, FOURTH DAY (EXPRESSED AS A PERCENTAGE OF NORMAL ADULT PROTHROMBIN ACTIVITY). 100 CASES

PERCENTAGE OF NORMAL ADULT PROTHROMBIN ACTIVITY	FOURTH DAY OF LIFE	
	CONTROL CASES	VITAMIN K CASES
10- 20	1	-
20- 30	4	-
30- 40	6 } 26	1 } 6
40- 50	7	-
50- 60	8	5
60- 70	17	6
70- 80	29	13
80- 90	15	18
90-100	8	21
100-110	4	26
110-120	1	7
120-130	-	3
Total	100	100
Mean	72.4% of normal	93.3 per cent of normal

28, and 35 per cent, respectively, of normal on the fourth day had bloody stools or vomited small amounts of bloody mucus on the same or on the following day. Hemorrhage did not occur in any infant whose prothrombin was normal on the fourth day. Four infants whose mothers received the drug less than an hour before delivery had clotting activity values similar to those of the control group. It, therefore, seems reasonable to conclude that the drug should be administered at least one hour before delivery if any beneficial effect is to be obtained.

The results in this part of our investigation seem to indicate that vitamin K prevents the hypoprothrombinemia which normally occurs from the second to the fourth or fifth day of life. They also indicate, as has been suggested by Quick,[24] that hemorrhagic disease of the newborn may be due to a failure of the plasma prothrombin levels to return to normal.

PART II

The second part of our investigation was undertaken to show the truth or falsity of the foregoing conclusions by observing the change in the incidence of hemorrhagic conditions which might follow the administration of vitamin K to a fairly large number of parturient women.

Two milligrams of 2-methyl-1, 4-naphthoquinone (Thyloquinone) were given to alternate mothers in a series of 2,059 cases. Of these, 1,037 were used as controls and 1,022 received vitamin K. Because some of the patients were too far advanced in labor at the time of admission to be of value in the vitamin K study, the control group contained 15 more cases than the vitamin K series.

Table V shows the site of hemorrhage and also gives the type of delivery and weight of the control infants. The same data are recorded for the vitamin K cases in Table VI. A summary showing the incidence of hemorrhage in the full-term and premature infants of both series is furnished in Table VII. In the control group of 1,037 cases, 21, or 2 per cent, revealed some evidence of hemorrhage, while only 5, or 0.5 per cent, of the 1,022 vitamin K cases had any signs of bleeding. From our clinical observations in this large series of cases, therefore, it would seem that the use of vitamin K during labor reduced the incidence of hemorrhage in the newborn infant approximately 75 per cent.

TABLE V. HEMORRHAGIC CONDITIONS OBSERVED IN 1,037 CONTROL INFANTS

NO.	TYPE OF DELIVERY	WEIGHT (GRAMS)	SITE OF HEMORRHAGE
1	Spontaneous	1680	Intracranial hemorrhage
2	Spontaneous	3140	Bloody stools two days
3	Spontaneous	2560	Intracranial hemorrhage
4	Spontaneous	3640	Bloody stools fourth day
5	Low forceps	3000	Intracranial hemorrhage
6	Spontaneous	2940	Intracranial hemorrhage
7	Spontaneous	1620	Intracranial hemorrhage
8	Spontaneous	2620	Bloody stools sixth day
9	Spontaneous	2960	Intracranial hemorrhage
10	Spontaneous	1780	Intracranial hemorrhage
11	Spontaneous	3580	Bloody stools third and fourth days
12	Spontaneous	2500	Intracranial hemorrhage
13	Breech	1160	Intracranial hemorrhage
14	Spontaneous	3100	Bloody stools third to fourteenth day
15	Spontaneous	3160	Intracranial hemorrhage
16	Breech	3560	Intracranial hemorrhage
17	Spontaneous	3180	Bloody stools fourth day
18	Breech	1590	Intracranial and adrenal hemorrhage
19	Spontaneous	2900	Intracranial hemorrhage
20	Spontaneous	2560	Intracranial hemorrhage
21	Spontaneous	4200	Bloody stools second, third, fourth, and fifth days

TABLE VI. HEMORRHAGIC CONDITIONS OBSERVED IN 1022 VITAMIN K INFANTS

NO.	TYPE OF DELIVERY	WEIGHT (GRAMS)	SITE OF HEMORRHAGE
1	Low forceps	3500	Intracranial hemorrhage
2	Spontaneous	2920	Intracranial hemorrhage
3	Spontaneous	3200	Bloody stools third day
4	Cesarean section Placenta previa	1880	Intracranial hemorrhage
5	Spontaneous	1840	Intracranial hemorrhage

TABLE VII. SUMMARY OF END-RESULTS FOLLOWING THE USE OF VITAMIN K DURING LABOR

	CONTROL CASES		VITAMIN K CASES	
	NO. OF INFANTS	HEMORRHAGE CASES	NO. OF INFANTS	HEMORRHAGE CASES
Full term infants	981	16 or 1.6%	985	3 or 0.3%
Premature infants	56	5 or 9.0%	37	2 or 5.4%
	1037	21 or 2.0%	1022	5 or 0.5%

Since no ill-effects were observed from the administration of this preparation to any of our patients, we are now giving 2 mg. of vitamin K at the time of admission and are repeating the dose at six-hour intervals throughout the labor. In this way, we hope to facilitate the transmission of the drug in amounts sufficient to assure the presence of adequate prothrombin activity in all newborn infants. Because the tendency to diminished clotting activity is greater in prematurely born children, it is our custom to repeat the drug every four hours in all premature labors. We hope by this means to reduce the all too frequent

incidence of hemorrhage in infants born before term, and we anticipate as a result a considerable reduction in the death rate of our prematurely born infants.

SUMMARY AND CONCLUSIONS

1. Clotting activity was studied on the first, second, and fourth days of life in a series of 200 infants. Vitamin K was given during labor to the mothers in alternate cases. We were able, therefore, to compare the effects of its administration in 100 cases with a similar number of controls.

2. A study of the control infants shows that, on the first day of life, clotting activity is approximately 70 per cent of that which is observed in normal adults.

3. A physiologic fall in prothrombin usually occurs on the second day. This fall at times may reach dangerously low levels.

4. Fifty per cent of the infants whose clotting activity fell below 35 per cent of normal values showed evidence of hemorrhage.

5. By the fourth day, clotting activity values tend to approach the level of those observed on the first day of life and are said to reach this level by the sixth day.

6. Clotting activity approaching that observed in the normal adult may be obtained on the first day by the prophylactic administration of vitamin K to the mother during labor.

7. Vitamin K, administered to the mother during labor, also prevents the physiologic fall in prothrombin values which is commonly observed on the second day of life.

8. Only one infant in a series of 100 whose mothers received vitamin K during labor, had a low value for clotting activity and, in this instance, it was 38 per cent of the normal adult value on the fourth day only.

9. The use of vitamin K during labor and antenatally should prevent some of the hemorrhages which occur in the newborn infant.

10. Only 5, or 0.5 per cent, of 1,022 infants whose mothers received vitamin K showed any evidence of hemorrhage in contrast with 21, or 2 per cent, of 1,037 control cases.

11. In this series of 2,059 cases, the alternate mothers of which received vitamin K, it appears that this drug reduced the incidence of hemorrhage approximately 75 per cent in the newborn infant.

12. Vitamin K, accordingly, should be very valuable in reducing the incidence of hemorrhage in all newborn infants. This should be especially true when they are born prematurely or after long labors and difficult operative procedures.

We wish to express our thanks to Drs. W. B. Henderson, D. A. Connors, and L. E. Mendonsa, residents on the College divisions at Kings County and Greenpoint Hospitals, for their assistance in the conduct of these investigations.

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DISCUSSION

DR. E. STEWART TAYLOR (by invitation).—The important thing that should be emphasized is that 50 per cent of the control infants, who had a clotting activity below 35 per cent of normal, had hemorrhage of some variety. On the other hand, in the 100 vitamin K cases, there was only one which had a low prothrombin clotting value and no case showed evidence of hemorrhage.

DR. ARCHIE BLACK (by invitation).—There seem to be two important sources of vitamin K in Nature, one from foods, particularly the green vegetables, such as spinach and alfalfa, and the other from bacteria. Apparently, the bacteria in the intestinal tract contribute considerably. It has been suggested by Quick and several others that the prothrombin content of the blood of the newborn infant begins to rise from the third to the fifth day, because it requires that long for the bacterial flora to be established in the intestinal tract and to produce sufficient vitamin K.

The known vitamin K's that exist in Nature are all chemical derivatives of 2-methyl-1, 4-naphthoquinone. It was a very interesting discovery that this simple compound is more active than either of the two vitamins found in Nature, the one from alfalfa and spinach and the other which is produced by bacteria.

DR. CARL T. JAVERT (by invitation).—The evaluation of the prothrombin concentration in the blood, from the standpoint of various tests, including the older one of Howell, gives values with great apparent variance. If you use the Smith or the Quick test, you find relatively normal or slightly subnormal values in the prothrombin level in the blood of the infant. On the other hand, if you use the Warner, Brinkhouse, and Smith test, the two-stage test which was referred to, you find that the prothrombin level in the cord blood of newborn infants is decidedly low. In relation to an adult with 100 per cent of normal, the newborn infant may have as little as 20 per cent.

It is surprising that many infants with a low prothrombin do not develop hemorrhagic disease. We have seen levels as low as 5 per cent of normal and less, in terms of the Warner, Brinkhouse, and Smith test, without hemorrhagic disease.

It was interesting to me to see in the control cases of this series that there was an incidence of hemorrhagic disease as high as 2 per cent. In our own clinic the average incidence of hemorrhagic disease is about the same as in Dr. Beck's vitamin K treated patients, namely, 0.7 per cent. This incidence is borne out by observations of Townsend as far back as 1894, and more recently by Salmonson in Norway, as well as by reports from other parts of the world. With an incidence of hemorrhagic disease of 1 per cent or less, the effectiveness of vitamin K or any other preparation for the further reduction of the incidence of hemorrhagic disease may

be difficult to prove. Prolonged labor is of great significance. We found in a study of at least 700 infants delivered by cesarean section that there were no cases of hemorrhagic disease in the infants delivered without labor. The mother of one infant had sixty hours of labor before delivery, and this infant developed hemorrhagic disease. That creates the interesting hypothesis that even if all infants have a low prothrombin level at birth, there is still necessary a second factor, namely the trauma of labor. All infants then, of mothers with a prolonged labor, will probably be benefited by the antenatal administration of vitamin K to the mother.

DR. ONSLOW A. GORDON.—I would like to ask Dr. Beck how much vitamin K was given and when it was given during the course of labor.

DR. SAMUEL A. WOLFE.—I would like to ask if vitamin K is of any value in cerebral hemorrhage of the newborn infant if the prothrombin level is above 40 per cent of the average value.

DR. I. C. RUBIN.—I would like to ask Dr. Beck if he has found a single case of erythroblastosis in his series, and if not, would he venture any expression of opinion with regard to the administration of vitamin K in such cases if met with?

DR. ARCHIE BLACK.—The possibility of hyperprothrombinemia from excessive amounts of vitamin K has been raised. As far as I know, no evidence has been reported of the existence of such a condition. Some of the European workers have administered very large doses of this naphthoquinone to human beings, in some instances one hundred times as much as Dr. Beck has used, and they have not observed any such condition.

DR. BECK (closing).—You may recall that in my paper I stated that different results are obtained when the various tests are used. This, however, has no bearing as far as our observations are concerned, since we used the same test throughout all of our work. We did have a relatively high incidence of hemorrhage cases. These were not typical cases of melena neonatorum but in all of them a diagnosis of bleeding of some character was made. In our Clinic, we observed a rather high incidence of these bleeding cases long before we knew anything about vitamin K. Because a very large proportion of our service patients were in the low economic group, we thought that this bleeding tendency might be due to some dietary deficiency. Since we have been using vitamin K, on the other hand, there has been a great diminution in the same types of hemorrhage. As both vitamin K cases and the control series were analogous in other respects, we believe that our results show the beneficial effects of vitamin K; in spite of the fact that our control series had more hemorrhages than is usually observed in those clinics whose patients belong to the higher economic groups. I think this question of diet also accounts for the great difference between the incidence of bleeding in our private and ward patients. The private patients, as in Dr. Holladay's practice, no doubt received a balanced diet throughout their pregnancy and, as a result, were less liable to have this deficiency.

We gave 2 mg. of thyloquinone in the course of the labor. Its cost, I think, is about two cents per dose. As it can do no harm and may do considerable good, we think that it should be used routinely in private as well as ward cases. In most instances, it was given at least one hour before delivery. We recommend, however, that it might be better to administer the drug every six hours throughout the labor.

In answer to Dr. Bunzel's query concerning the criteria for hemorrhage, I would like to say that any type of bleeding was regarded as hemorrhage in the newborn infant. As our tabulations show, most of the hemorrhages were either intracranial or from the intestinal tract. In the majority of instances of intracranial hemorrhage, the diagnosis was made at autopsy. All diagnoses were made by the pediatricians and they did not know which mothers had received vitamin K. The same criteria and the same physicians therefore were used in both the control and the vitamin K cases. Our deductions, as a result, should be correct.

This preparation has been recommended for use during the ante-partum period by some men. We have been reluctant to use it at this time because of the increased coagulability of the blood which is noticed in cases of eclampsia. After the

pregnancy has reached term and the patient has gone into labor, we do not think that the administration of vitamin K should have any deleterious effect in this regard.

Vitamin K, I believe, was first used in infants after birth. Its hypodermic administration is very valuable in those cases in which the prothrombin values are low. It certainly should be used whenever hemorrhage occurs or whenever the type of delivery leads us to anticipate hemorrhage. In other words, after prolonged labors and operative deliveries, this prophylactic use of vitamin K should be of value. Because of the increased tendency toward hemorrhage in prematurely born infants, the prophylactic administration of vitamin K also is recommended whenever a child is born before term, even though it be delivered by cesarean section.

In reply to Dr. Wolfe, I would say that I doubt very much whether vitamin K would be of any use in the patient who has a high prothrombin value.

We have noted an increase in the incidence of erythroblastosis in our clinic. This may, of course, be due to the fact that we are on the lookout for this condition and, as a result, make better diagnoses than in former times. Because our patients belong in the low economic group, however, we have thought the increase in this condition also might be due to some deficiency. Replying to Dr. Rubin, I might say that one of the control cases had erythroblastosis. In this instance, however, there was no reduction in the prothrombin values.

FETAL ELECTROCARDIOGRAPHY AND STETHOGRAPHY

A Combined Study

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INTRODUCTION

AS FAR as we know, no attempt has been made to study the human fetal electrocardiogram and stethogram simultaneously. Bell,[1] in his discussion of the only twin pregnancy recorded by the fetal electrocardiogram, presents arguments to prove that the waves produced are fetal waves; and concludes his discussion with the statement that completely satisfying proof could be given only by simultaneous records of fetal heart sounds and fetal electrocardiograms.

Many contributions have been made and various methods used in the study of fetal heart sounds.[2-9] Originally, amplification of heart sounds was done on adults and its practicability was demonstrated. Pommerenke and Bishop[4] used an instrument for the amplification of fetal heart sounds with good room volume, clarity, and freedom from distortions. They were able to obtain sufficient output from the amplifier to cut satisfactory phonograph discs. DeCosta[5] was able to reproduce the rate and regularity of fetal heart sounds by means of the photostethoscope, an instrument consisting of a small neon lamp which translates sounds into flickers of light.

Electric stethoscopes, various microphones, thermionic valves, and amplifying and reproducing apparatus[6-9] have been used by many workers to demonstrate fetal heart sounds.

Although a great deal of work has been done with amplification of heart sounds (adult, child, and fetus), very few studies have been reported of the actual recording of these sounds by the stethograph or a similar instrument.

Recently, McKee[10, 11] reported interesting studies of heart sounds in normal children, and heart sounds and murmurs in children with rheumatic heart disease by means of the stethograph. Smith[12] studied fetal heart sounds in 52 cases by the use of a recording instrument, and was able to reproduce the amplified sounds by means of phonograph discs.

Originally it was shown that the electric energy of the fetal heart was too weak, in relation to that of the maternal heart, to be demonstrated on an electrocardiogram when usual methods were used. Therefore work was done on animals whose fetus was larger than the human fetus.

Nörr,[13] and Steffan and Strassman,[14] studied domestic animals especially the horse, and the latter developed a satisfactory technique which they used on pregnant women. There are a few scattered studies on the human fetal electrocardiogram by Sachs,[15] Maekawa and Toyoshima,[16] and Strassman.[17] In 1938, Strassman[18] and Mussey[19] were able to report on the improved technique and results of routine fetal electrocardiography during pregnancy. They studied 52 gravidas on whom 70 fetal electrocardiograms were taken, and found 87 per cent positive fetal electrocardiograms and 13 per cent negative tracings.

At about the same time (1938), Bell[1] studied a series of 33 cases of fetal electrocardiograms by using a fundus-symphysis pubis lead with the thermionic valve technique, a valve electrocardiograph to which a balanced input amplifier was introduced. This instrument gave as much amplification as could be obtained without oscillation. Of the 33 cases that he examined in the last two months of pregnancy, about one-third showed positive results. He suggests that the failure to secure positive results in all cases is due partly to the differences in the electric properties of the abdominal wall, and partly to the electrical disturbances produced by the abdominal muscles, and not to insufficient sensitivity of the apparatus or to differences between the fetus.

Occasional cases[20] have been reported of the accidental detection of fetal electrocardiograms while doing a routine maternal electrocardiogram.

PURPOSE

The purpose of this study is to develop a positive method by the use of a simple technique for determining during pregnancy and labor whether or not the fetus is alive. It occurred to us that if information concerning the status of the fetal heart could be gained by the recording of fetal heart sounds and fetal electrocardiograms individually, much more could be learned by a combined study, both for practical teaching and research purposes. Records obtained by any method should be accurate as well as easy to interpret.

With this in mind, the principles promulgated by Strassman[18, 19] for the study of the fetal electrocardiogram were adhered to in this combined study. These principles are: (1) To avoid modification of the electrocardiographic apparatus which was generally in use; (2) not to employ unusual leads, such as placing electrodes in the rectum or vagina, or fundus-symphysis pubis leads as used by Bell; (3) to increase the amplitude of the waves and decrease shakiness and fuzziness of the tracings as far as possible.

The physician not infrequently encounters conditions which make it difficult for him to hear the fetal heart sounds by ordinary methods. These conditions are: (1) An obese abdominal wall, (2) an excessive amount of amniotic fluid (hydramnios), (3) an abnormal position of the fetus in relation to the mother's abdominal wall, and (4) the presence of adventitious sounds (uterine souffle).

At other times, operative procedures (craniotomy and cesarean section) may be necessary, and determination of the viability of the fetus is most important. This determination may also be of importance from a medicolegal aspect where the availability of permanent graphic records is necessary.

Many other problems are encountered which may be answered by our combined study. These may include: (1) The presence of twins or multiple pregnancies, (2) the presence of congenital defects of the fetal heart, (3) the effect of pregnancy and labor on the fetal heart under normal and abnormal conditions, and (4) the effect of drugs on the fetal heart.

METHOD

The instrument used in this study is called the electrocardiograph-stethograph.* Tracings of the fetal electrocardiogram and stethogram can be made separately or simultaneously. In the technique for the study of the fetal electrocardiogram, we follow Strassman's method very closely with few exceptions.

The patient is placed flat on her back on a bed, thereby avoiding any muscular contractions that may occur in the sitting position. She is allowed to rest about fifteen minutes before any recordings are done, to permit her to become acclimated. She is assured that there is nothing wrong with her pregnancy in order to allay any anxiety. The room used for this study was carefully selected to avoid extraneous noises and other electrical apparatus which might interfere with the recording of fetal heart sounds and the fetal electrocardiogram. The skin and the electrodes are moistened with saturated saline solution. The electrodes used are the same as those used for routine electrocardiography, and measure 2½ by 1½ inches. The electrodes are placed on the upper arms and the left thigh, and are fastened with bandages 3 inches wide which have been previously soaked in saturated saline solution. The purpose of the position of the electrodes and the use of saline solution is to lessen the skin resistance and to improve the detection of the fetal cardiac impulses.

The stethograph of our instrument was designed by Lockhart and for a detailed review of methods, reference should be made to his papers.[21, 22] It is an instrument that records sound vibrations as they actually occur, rather than as they are heard. It consists mainly of a microphone, a stethophone, an amplifier, and a recorder. The microphone is equipped with three bells in order to secure various degrees of filtering. The No. 1 bell has a large open face measuring 2 inches in diameter, the No. 2 bell is similar in size but covered with a diaphragm, the No. 3 bell is approximately of the same size as that used on stethoscopes. After trying all three bells, we found that the fetal heart tones can be recorded with the greatest amplitude by the No. 1 bell.

The following is the routine used in the stethographic recording: (1) Listen to the abdomen with the ordinary stethoscope in order to localize the fetal heart sounds; (2) if detected, apply the microphone to that particular area, and hold it in place by means of a rubber belt. The rubber belt must be tight enough to insure a good seal between the bell and skin; (3) listen with the stethophone, clarify the fetal heart sounds by means of the volume control, avoid picking up room noises, and prevent blurring of the light beam shadow; (4) if unable to

*Manufactured by the Cambridge Instrument Company as the Hindle "All Electric" Model Mobile Electrocardiograph-Stethograph.

detect fetal heart tones with the ordinary stethoscope, apply the microphone to all four quadrants of the abdomen, listening at each quadrant by means of the stethophone for fetal heart sounds. By this method we were able to detect sounds in almost all cases; (5) if no sounds are detected, record a tracing from each quadrant; and (6) if sounds are detected, record a tracing from that particular area.

Having completed all connections, the fetal electrocardiogram and stethogram are recorded separately and simultaneously. In routine electrocardiography, the speed of the film is 25 mm. per second. This speed is used for the simultaneous recording. Ordinarily, a speed of 50 to 75 mm. per second is used in stethography. We used this speed in studying the heart sounds separately.

Electrocardiographic tracings are first taken with the usual leads (I, II, and III). The electrode is then changed from the left thigh to the right thigh, and the tracings are repeated with Leads II and III (right arm-right thigh, left arm-right thigh, respectively). These five leads (right arm-left arm, right arm-left thigh, left arm-left thigh, right arm-right thigh, left arm-right thigh) cover the main directions the axis of the fetal heart might take in the body of the mother, projected on a two dimensional field. The usual electrocardiographic standardization is used; 1 millivolt deflects the string 1 cm. Two feet of film are used for each lead in order to facilitate study of the tracings.

It is a general physiologic fact,[23] that the first sound in adults is heard very shortly after the beginning of systole and the second sound immediately after the end of systole. The first sound is therefore systolic, and the second sound diastolic. In the stethograms studied, the systolic phase is measured from the beginning of the first sound to the end of systole, and the diastolic phase, from the beginning of the second sound to the end of diastole.

MATERIAL

This paper is a preliminary report of the study of the fetal electrocardiogram and stethogram during pregnancy. In a subsequent paper we will report on the results during labor, and add more cases during pregnancy.

Forty gravidas were drawn at random from the outpatient obstetric clinic. We had no previous knowledge of the location of the fetal heart, the presentation of the fetus, or the presence or absence of a viable fetus. None of the patients were organic cardiacs, although no attempt was made to discriminate. All patients were in the last two months of pregnancy because of previous knowledge[18, 19] that better results are obtained with the fetal electrocardiogram, although fetal heart sounds can be recorded as early as the sixteenth week of pregnancy. The patients were studied the day following their last visit to the obstetric clinic in order to correlate the findings of the obstetrician with our own.

After delivery, all necessary data relative to the baby were collected and recorded, as well as the final diagnosis at delivery.

Table I shows the age distribution and parity of the gravidas studied. It is noted that most of the patients are primiparas and in the younger age group.

TABLE I. DISTRIBUTION OF PATIENTS ACCORDING TO AGE AND PARITY

AGE	PARA I	PARA II	PARA III	PARA V	TOTAL
19-23	17	3	1	0	21
24-28	6	4	4	0	14
Over 28	0	4	0	1	5
Total	23	11	5	1	40

RESULTS

All 40 women gave birth to live babies. The stethogram was positive in all, or 100 per cent. In 4 cases the fetal heart tones could not be detected by the ordinary stethoscope. In these there was a loud uterine souffle which interfered with

detection by the ear. In one of the above cases, the patient was very obese. The uterine souffle was recorded together with the fetal stethogram in 13 cases, the souffle overlapping fetal systole and diastole. In one case the fetal heart sounds could neither be detected by the ordinary stethoscope nor by the stethophone (microphone), due to a very loud uterine souffle. The sounds were recorded by the stethogram (Fig. 5, *A*). Fetal sinus arrhythmia was present in 4 cases, and fetal movements were well recorded in two (Figs. 1 and 2).

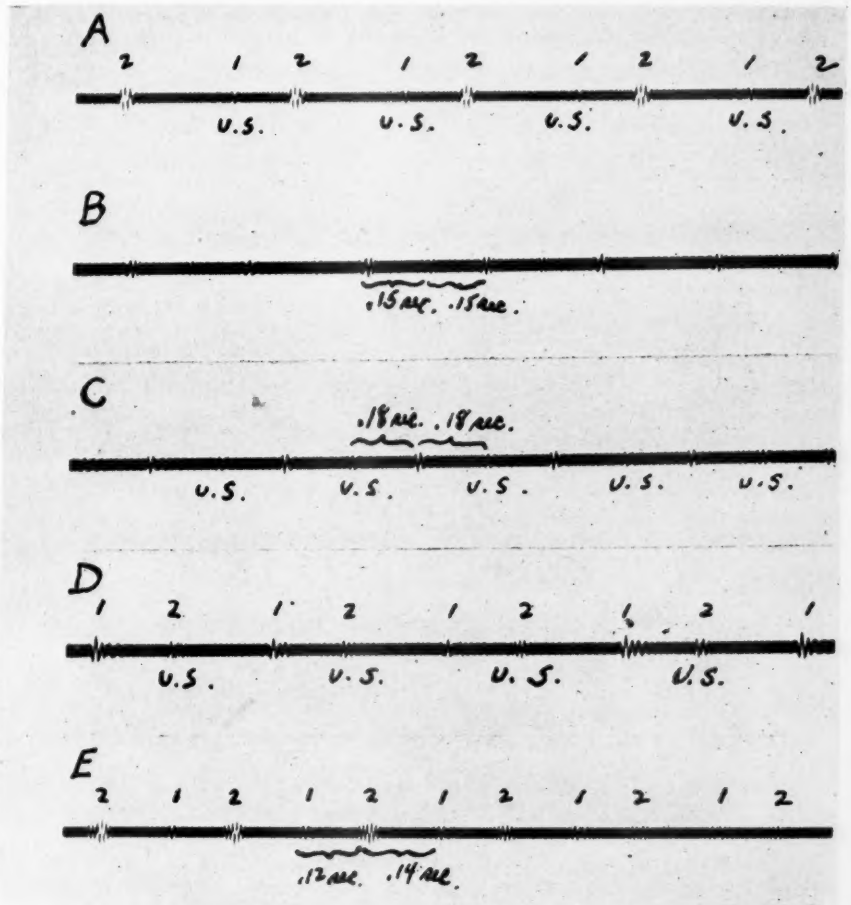

Fig. 1.—Normal fetal heart sounds with film speed of 50 mm. per second. *A*, second sound louder than first. Uterine souffle (*U.S.*) covers systole and diastole. Systole, 0.16 sec.; diastole, 0.27 sec. Fetal rate, 136. *B*, systolic and diastolic phases of equal length, 0.15 sec. Fetal rate, 200. *C*, systolic and diastolic phases of equal length, 0.18 sec. Fetal rate, 166. Uterine souffle covers both phases. See Fig. 3 for differentiating first from second sound. *D*, first sound louder than second. Note variations in intensity and length of sounds. In third cycle, intensity of first and second sounds appears equal. Systole, 0.20 sec.; diastole, 0.26 sec. Fetal rate, 130. Uterine souffle present. *E*, at the beginning of tracing, second sound louder than first. Near the end, intensities of both appear equal.

The length of fetal systole varied between 0.12 and 0.22 second and fetal diastole between 0.14 and 0.38 second. In 4 cases, the length of systole was equal to that of diastole. In these, the fetal heart rates were 200, 166, 166, and 150 beats per minute, indicating that the more rapid the fetal rate, the shorter the diastole, until systole and diastole may become equal (Fig. 1). This well conforms with the shortening of diastole in tachycardias of adults. In no event

was fetal systole greater than diastole. Fetal heart rates above 160 are considered abnormal.[31]

Of the 40 recorded stethograms, the second sound was loudest in 21 (55 per cent), the first sound in 7 (17½ per cent); they were equal in 9 (22½ per cent), and they were variable in 2 (5 per cent), the intensity of sounds varying in different cycles.

In 2 cases, the fetal heart sounds were hardly detectable by the stethogram. In one of these, the fetal electrocardiogram was hardly detectable, and the weight at birth was 5 pounds. The other was an infant delivered by breech which weighed 6 pounds 14 ounces. The size of the fetus may be a factor in the intensity of fetal heart tones.

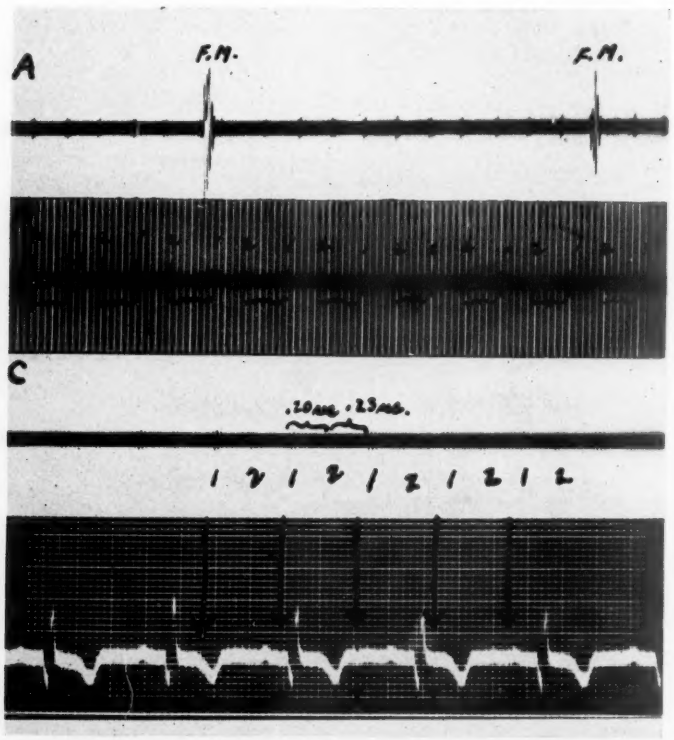

Fig. 2.—Normal fetal heart sounds with film speed of 25 mm. per second. *A*, active fetal movements (*F.M.*). Intensity of sounds appears equal. *B*, sinus arrhythmia. Note differences in the length of the various diastolic phases (compare diastolic phase of cycle 3 with that of cycle 6). Intensity of sounds varies; second is louder but toward end of tracing they appear equal. *C*, simultaneous recording of fetal heart sounds and fetal electrocardiogram. Note fuzzy electrocardiogram tracing but negative fetal waves (vertex presentation), detected with the aid of first sound. First sound louder than second.

There is a definite relationship between maternal and fetal heart rates. The fetal rate is in direct proportion to the maternal rate. The faster the maternal rate, the faster the fetal rate; the slower the maternal rate, the slower the fetal rate. The usual proportion of maternal to fetal pulse in our series is 3:5 or 5:8.

Of the 40 gravidas studied, 34 (85 per cent) were vertex presentations, and 6 (15 per cent) were breech presentations. Fetal electrocardiograms were positive in 32 cases (80 per cent), and were negative in 8 cases (20 per cent). In 27 (79 per cent) of the vertex cases, the fetal electrocardiograms were positive, and in 7 (21 per cent) they were negative. Five of the breech cases were positive

TABLE II. TIME BEFORE DELIVERY FETAL ELECTROCARDIOGRAMS TAKEN AND RESULTS OBTAINED

DAYS BEFORE DELIVERY	TOTAL RESULTS					VERTEX PRESENTATION					BREECH PRESENTATION				
	TOTAL EKG.	POSITIVE		NEGATIVE		TOTAL EKG.	POSITIVE		NEGATIVE		TOTAL EKG.	POSITIVE		NEGATIVE	
		CASES	%	CASES	%		CASES	%	CASES	%		CASES	%	CASES	%
0-20	25	20	80	5	20	22	18	82	4	18	4	3	75	1	25
21-67	15	12	80	3	20	12	9	75	3	15	2	2	100	0	0
Total	40	32	80	8	20	34	27	79	7	21	6	5	83	1	17

(83 per cent), and one was negative (17 per cent). These figures are slightly less than those of Strassman's series with the exception that our breech cases showed more positive electrocardiograms. We encountered no difficulty in studying breech electrocardiograms (Table II).

There is no difference in the percentage of positive fetal electrocardiograms, whether taken three weeks before delivery or later, provided they are recorded within the last two months of pregnancy. However, there is a definite relationship between the size of the fetus (as evidenced by birth weight) and the number of positive fetal electrocardiograms. The smaller the fetus, the less positive and more negative electrocardiograms are recorded. The larger the fetus, the more positive and less negative electrocardiograms are recorded. The sex of the fetus has no influence on the number of positive electrocardiograms (Table III).

TABLE III. RELATIONSHIP BETWEEN SEX, WEIGHT OF BABY AT BIRTH, AND POSITIVE FETAL ELECTROCARDIOGRAMS

WEIGHT	M.	F.	POS. EKG.	NEG. EKG.	% POS.	% NEG.
5 pounds to 7 pounds 8 ounces	11	7	13	5	72	28
7 pounds 9 ounces to 9 pounds 13 ounces	15	7	19	3	86	14
Total	26	14	32	8	80	20

Of the 5 positive breech cases with electrocardiograms, recorded 45, 28, 17, 12, and 9 days before delivery, two (seventeen and twelve days) eventually delivered as right occiput posterior. In both of these cases, the obstetrician's diagnosis concurred with our electrocardiographic findings, although roentgenograms taken five days before delivery showed vertex presentations. The one negative breech electrocardiogram was diagnosed as a breech by means of the microphone, which located the fetal heart in the left upper quadrant, although the obstetrician's diagnosis was left occiput anterior. This patient eventually delivered a fetus in the left sacral anterior position.

The number of positive tracings was almost the same in Lead II (right arm-left leg) and Lead IV (right arm-right leg) as compared with Lead III (left arm-left leg) and Lead V (left arm-right leg). In other words, the positive tracings in all four leads were approximately the same (Table IV). This coincides with the final diagnosis of 18 right vertex positions and 18 left vertex positions. In Strassman's series, there were more left vertex positions, and, therefore, positive tracings were highest and almost the same in Leads III and V, because these leads are the most favorable for recording impulses from the fetus in the left vertex position; whereas Leads II and IV are most favorable for recording impulses from the fetus in the right vertex position. As a rule, the left vertex position occurs more frequently than the right.

The ratio of the total number of positive tracings to the total positive electrocardiograms is practically the same, irrespective of the time they were taken before delivery. This again proves our previous contention that it is not the time before delivery but the size of the fetus that determines the number of positive tracings (Table IV).

TABLE IV. RELATIONSHIP BETWEEN THE TIME BEFORE DELIVERY, NUMBER OF POSITIVE ELECTROCARDIOGRAMS, AND NUMBER OF POSITIVE TRACINGS

DAYS BEFORE DELIVERY	TOTAL POS. EKG.	POSITIVE TRACINGS					
		LEAD I	LEAD II	LEAD III	LEAD IV	LEAD V	NO. POS. TRACINGS PER EKG.
0-20	20	1	15	12	14	11	2.6
21-67	12	0	5	8	8	6	2.3
Total	32	1	20	20	22	17	2.45 Av.

Although twins were suspected by the obstetrician in 2 cases, we were able to disprove this by the fetal electrocardiogram and stethogram. Follow-up verified our results. Unfortunately no opportunity of recording multiple pregnancies has been presented. Bell has the only positive tracing of twins on record.

DISCUSSION

The association of irregularities of rhythm, murmurs of the fetal heart, and pronounced slowing of the rate may in occasional instances be due to congenital heart disease, and the diagnosis can be made before delivery.[24] None of our cases of sinus arrhythmia or normal rhythm showed any stethographic evidence of congenital heart disease. All hearts examined after birth were normal. Sampson, McCalla, and Kerr,[25] working on phonocardiography of the human fetus, reported 31 cases of fetal cardiac irregularities, but in only one instance was there a congenital heart lesion. Sinus arrhythmia is a common finding in fetal hearts. It has no clinical significance, and is explained on the basis of a myogenic or a neurogenic origin, due to a relatively unstable pacemaker.

Of the 13 cases of uterine souffle recorded, 6 were on the left and 7 on the right side. This coincides with the equal number of right and left vertex positions in our series. The uterine souffle is a humming, blowing, rushing, sibilant, or even musical sound synchronous with the maternal heart. It originates in the large vessels, arteries and veins in the sides of the uterus. It is heard best on the lower left side of the uterus, but may be heard on the right side, anteriorly on both sides, and occasionally all over the abdomen. It may be loud, drowning the fetal heart tones as demonstrated in 4 of our cases, or soft, hardly audible, and even absent in some cases (10 per cent).[26] It may be heard at one time and be absent in the same place later. Some of our tracings show the above characteristics. It is usually systolic but may be both systolic and diastolic. It is found whether the fetus is dead or alive, and is not a diagnostic sign of pregnancy because it is heard over rapidly growing tumors.

Heart sounds consist of mixtures of frequencies or noises. They are never pure musical notes having single frequencies. The dominant frequencies of the various sounds tend to remain the same in each individual, regardless of the cardiac rate or of the sites at which the microphone is placed. The frequency composition[29, 30] of fetal heart sounds is similar to that of adult heart sounds. The amount of sound energy is, however, considerably smaller than for adult hearts. Since in certain cases, the ear is incapable of detecting fetal heart sounds, it is obvious that obstetric auscultation requires acuity of hearing at low frequencies. The absolute and relative intensities of sounds change greatly when the microphone is moved from one place to another, and when the heart rate changes.[10] This is demonstrated by placing the microphone at the apex or base of the adult heart. The intensity of fetal heart sounds depends upon the site at which the microphone is placed, as well as upon maternal and fetal conditions which may interfere with the transmission of sound. These conditions include thickness of the abdominal wall, change in position and movements of the

fetus, and the site of maximal intensity. The more rapid the fetal heart, the greater the intensity of its sounds.

Since the intensity of fetal heart sounds may vary, it may be difficult to differentiate the first from the second sound in the presence of systole and diastole of equal length. Under such conditions, the presence of a positive fetal electrocardiogram would help, since the R-wave of the electrocardiogram precedes the first heart sound by a few hundredths of a second (usually 0.04 sec.) (Figs. 2 and 3). A similar relationship occurs in adults with the simultaneous recording of the electrocardiogram and stethogram.

Although it has been proved that the larger the fetus, the slower the rate, the smaller the fetus, the faster the rate, it appears that the maternal rate has a definite influence over the fetal rate in spite of the size of the fetus. The difference in rate may be a helpful differential point between a large fetus and twins.[27]

Strassman[18] has shown that the impulses of the fetal heart are too weak to give in a visible way the same configuration of heart action that is found in the electrocardiogram of adults. The P- and T-waves are absent. The R-wave is the only visible part of fetal heart action during pregnancy and labor. The simultaneous recording of the fetal electrocardiogram and stethogram works both ways to prove that the R-wave is the only deflection. It precedes the first sound of the fetal heart and the first fetal heart sound follows it. The amplitude of the R-wave varies between ½ and 2 mm., and its width between 0.02 and 0.04 sec. It is usually visible to the trained naked eye but sometimes a magnifying glass is necessary for identification.

In order to determine if a fetal electrocardiogram is positive, the following criteria are essential: (1) The R-wave must be followed throughout the entire lead; (2) it must occur at more or less regular intervals; (3) the interval must correspond in length to the distance between each fetal heart beat as recorded on the stethogram; and (4) the exact fetal heart rate as determined by the distance between two fetal waves must correspond to the rate as determined by the fetal stethogram. In determining the fetal heart rate, the same method is used as in adult electrocardiography.

Since in vertex presentation, the fetal heart is upside down in relation to the maternal heart, the fetal R-wave appears as a negative wave deflected below the isoelectric line, and is sometimes followed by a very short positive wave (Figs. 3 and 4). In breech presentation the opposite takes place, a positive R-wave is followed at times by a short negative wave (Figs. 5 and 6). There was no difficulty in studying either the positive or negative waves, because in all tracings, fetal waves are better detected on the isoelectric line than on any of the maternal waves. When the fetal waves coincide with the maternal QRS complex, they are never visible. When they coincide with the maternal P- and T-waves, they are hardly visible.

We wish to detail Case 36, a positive breech electrocardiogram, as one of the most unique fetal tracings ever recorded (Fig. 6). There is no fetal electrocardiogram on record in which the waves are recorded in Lead I. Theoretically, it is assumed that the tracing in Lead I is positive only in cases of transverse

position of the fetus, because in longitudinal positions (vertex or breech presentation), the axis of the fetal heart is vertical, and, therefore, the isoelectric zones are horizontal and parallel to Lead I (right arm-left arm). In this case of right sacral anterior, there are positive or upright fetal waves in Leads I, II, and IV.

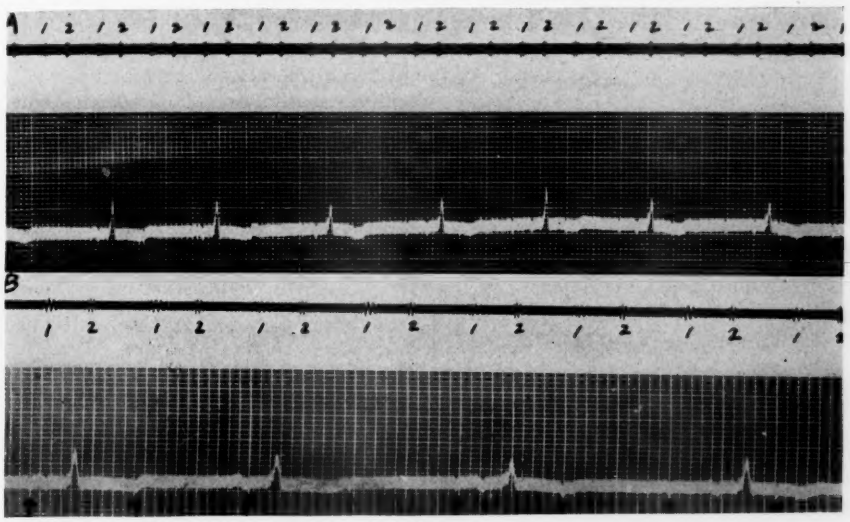

Fig. 3.—Simultaneous recording of fetal heart sounds and fetal electrocardiogram. *A*, speed of film is 25 mm. per second. Note definite relationship between the first sound and the R-wave of the fetal electrocardiogram. Arrows indicate inverted or negative R-waves (vertex presentation). Second sound is louder than first sound. *B*, same as *A*, except that speed of film is 50 mm. per second.

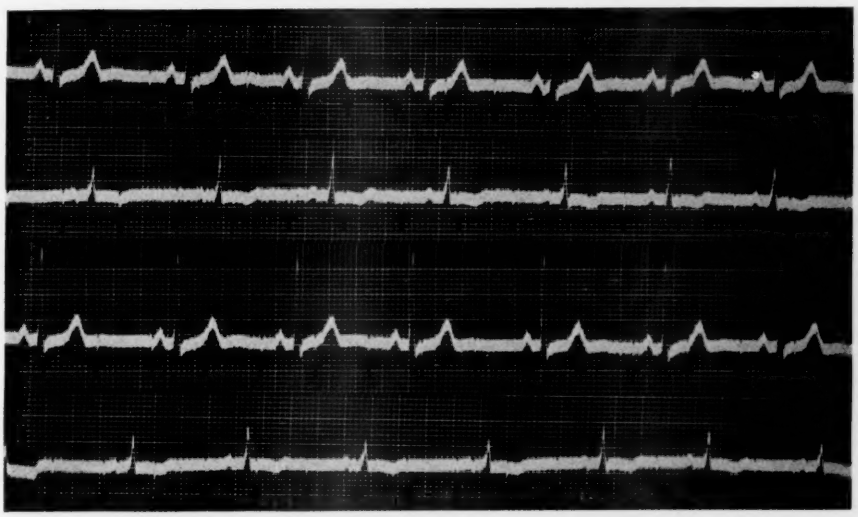

Fig. 4.—Fetal electrocardiogram, Leads II, III, IV, and V. Arrows indicate fetal waves (R-waves) which are inverted or negative, indicating vertex presentation. Note that fetal waves are excellent in spite of fuzzy tracing.

The only reason we can advance for the positive Lead I, is that the fetus was in an oblique position, with the axis of the fetal heart transversely and parallel to Lead I. The electrocardiographic diagnosis is a transverse heart and a breech presentation. Another interesting feature of this case is the presence of a fetal

heart rate that not only approximates the maternal rate, but even becomes slower than the maternal rate. In Lead I, the maternal rate is 125 (sinus tachycardia), and the fetal rate is 94. At the beginning of Lead II, the maternal rate is 150 (marked sinus tachycardia), and the fetal waves are not detected, due to the marked sinus tachycardia. As the maternal rate slows down in this lead to 83, the fetal waves are detected and the fetal rate is still 94 beats per minute. At the beginning of Lead IV, the maternal rate is now 65 and the fetal rate slows down to 83. Toward the end of Lead IV, the maternal rate becomes 75 and the fetal rate still remains at 83. The above variations in rate were temporary, because the fetal rate at birth was 140. It seems that the mechanism involved in the above rate changes affected not only the mother but also the fetus. Whether the fetal heart rate was chiefly influenced by the maternal rate and vice versa, or both were separately affected, is difficult to state. One can simply imply that the condition was undoubtedly a temporary sympathetic-vagal disturbance affect-

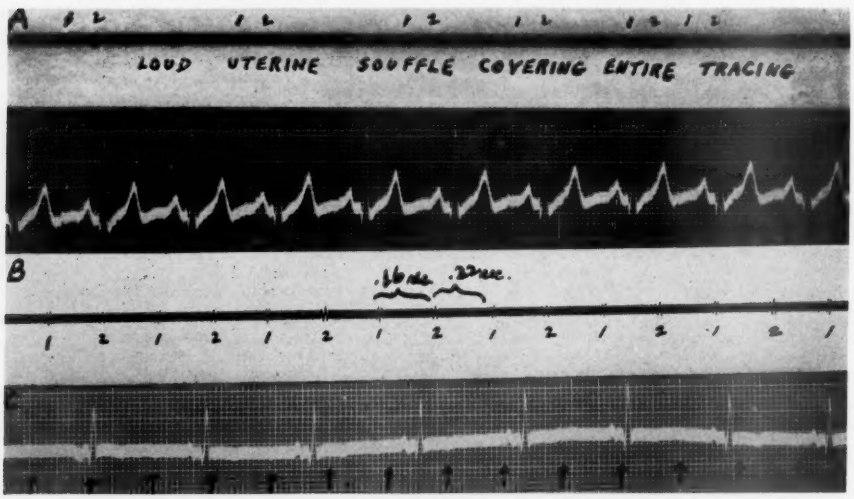

Fig. 5.—Simultaneous recording of fetal electrocardiogram and stethogram. *A*, fetal sounds are covered by a loud uterine souffle, making it difficult to detect and differentiate the sounds. Second sound is louder. Fetal waves help to distinguish the sounds and vice versa. Arrows indicate upright or positive waves (breech presentation). Film speed is 25 mm. *B*, fetal heart sounds with film speed of 50 mm. Note variations in intensity of the sounds. *C*, same case as *B*, except that the fetal electrocardiogram has a film speed of 25 mm. Arrows indicate inverted or negative fetal waves (vertex presentation).

ing both mother and fetus. In the fetus, it was a sinus bradycardia or possibly a temporary heart block, and in the mother it was a sinus tachycardia. There is no doubt of the uniqueness of this case from every standpoint. Although the baby was discharged as normal at birth, a follow-up study will be made.

Conditions sometimes arise (infections, hyperthyroidism, etc.) in in which the maternal rate becomes rapid, making it difficult to differentiate maternal from fetal rate. In such instances, Lönne[32] suggests the simple procedure of taking a deep breath after quiet breathing, and holding it. Thus one approaches the physiologic rate, whereas the fetal rate is not disturbed. In our unique case, it would have been difficult to differentiate maternal from fetal rate without the use of the fetal electrocardiogram.

In evaluating the cause of our 8 negative fetal electrocardiograms, several factors are involved. Two cases (twenty-seven and twelve days

before delivery) gave excellent tracings but both showed a maternal sinus tachycardia and one a fetal sinus arrhythmia. Four cases (twenty-one, eleven, five, and two days before delivery) gave excellent tracings, but the size of the fetus was in the lower weight group. In the last 2 cases (twenty-five and eight days before delivery), the patients were very nervous, and the tracings showed evidence of interference due to muscle tremor. One of these cases was also in the lower weight group.

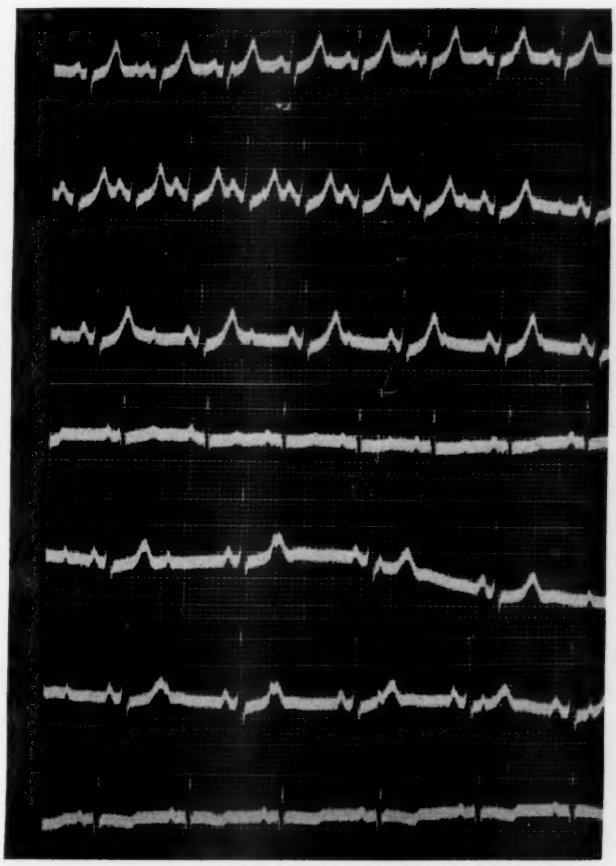

Fig. 6.—Fetal electrocardiogram, Leads I, II, IV. Arrows indicate upright or positive waves (breech presentation). For full description see text.

Of the 8 negative cases, 5 were in the lower weight group. In addition to the weight of the fetus, nervous patients, maternal sinus tachycardia, and possibly fetal sinus arrhythmia may be factors in the causation of negative electrocardiograms.

CONCLUSIONS

It is interesting to note that the diagnosis of position, by location of the fetal heart by means of the microphone, is more accurate than the obstetrician's diagnosis (by ordinary methods), when compared with the final diagnosis on delivery. This comparison is made with due con-

TABLE V. RELATIONSHIP BETWEEN LOCATION OF FETAL HEART, OBSTETRICIAN'S DIAGNOSIS, AND FINAL DIAGNOSIS ON DELIVERY

DAYS BEFORE DELIVERY	POSITIVE EKG.		LOCATION OF F.H. BY MICROPH.				OBST. DIAGNOSIS				FINAL DIAGNOSIS			
	VERTEX	BREECH	R.L.Q.	L.L.Q.	R.U.Q.	L.U.Q.	R.O.	L.O.	R.S.	L.S.	R.O.	L.O.	R.S.	L.S.
0-20	18	3	11	11	1	2	8	15	1	1	11	12	1	1
21-67	9	2	7	7	1	0	12	3	0	0	7	6	2	0
Total	27	5	18	18	2	2	20	18	1	1	18	18	3	1

NOTE: Two positive breech presentations, by fetal electrocardiogram, delivered as right occipitoposterior position, and the one negative breech presentation delivered as a left sacral anterior position. This accounts for the discrepancy between the number of positive breech electrocardiograms and the final diagnosis.

sideration to the possible change of position before delivery (Table V). The most accurate method of detecting presentation is by means of a positive fetal electrocardiogram.

It is obvious, from our results, that the study of the fetal heart by the fetal electrocardiogram and stethogram, either separately or simultaneously, is the only method available at present for an accurate estimation of fetal life.

One cannot always depend on ordinary hearing for accurate results,[30] as well as one cannot at times depend on amplified hearing. But a recorded tracing of sounds can never fail, provided there is something to record. A contracting fetal heart muscle will always produce sounds which can be recorded by the stethograph or any similar instrument.[28] By the same token, fetal movements due to muscular contraction produce sounds which can be definitely recorded.

The method of sound recording gives us further information concerning the fetal heart. The first and second sounds, and the systolic and diastolic phases can be accurately studied. The presence of other sounds (third and auricular sounds), adventitious sounds (uterine souffle), cardiac murmurs (congenital heart disease), and irregularities of rate and rhythm (sinus arrhythmia, sinus tachycardia, sinus bradycardia, and congenital heart block), of the fetal heart beat can be visualized. The exact location of the fetal heart can be determined by the microphonic attachment. And finally, our series shows 100 per cent accurate diagnosis of fetal life by the stethogram and verified by 40 live babies at birth. Although there were no twins in our series, it would be interesting to study stethographic records under such conditions.

We believe that the technique for the detection of the fetal electrocardiogram has been well perfected by Strassman.[18, 19] The occurrence of a negative fetal electrocardiogram does not depend as much on the technique used as on the presence of other factors. We have conclusively proved in our series that the size of the fetus is an important factor, irrespective of the time before delivery, provided the electrocardiogram is taken within the last two months of pregnancy. We have suggested that maternal tachycardia and perhaps fetal sinus arrhythmia may be factors. A nervous patient will cause fuzziness of the tracing due to muscle tremor, and so become an important factor in a negative fetal electrocardiogram. Whatever the cause, we feel certain that the technique is not at fault.

The positive fetal electrocardiogram gives accurate information concerning fetal life as well as becoming an accurate aid in the diagnosis of fetal presentation. The mere presence of a positive tracing means a live fetus, whereas its absence does not signify fetal death, if certain factors mentioned above are present. If these factors are absent and the tracing is excellent, then fetal death should be considered and, of course, verified by the stethogram. The presence of a negative fetal wave means the presence of a vertex presentation at the time the tracing is taken. The presence of a positive fetal wave signifies the presence of a breech presentation at the time the tracing is taken. We were

fortunate in recording the only positive fetal waves on record in Lead I in a breech presentation. We advanced the reason for this paradox as due to the transverse position of the fetal heart in an oblique breech presentation.

The fetal electrocardiogram is indispensable in differentiating between first and second heart sounds, in the presence of equal systolic and diastolic phases caused by fetal tachycardia.

Its value also lies in the fact that a combined tracing of the maternal and fetal electrocardiograms can be studied, and used as a permanent record for medicolegal or other purposes.

There is no doubt of its value in twin pregnancies as shown by Bell's case, in which both waves were upright, proving the presence of two breech presentations. It is certainly of great help to the obstetrician to know in advance the presentation of twins so that he can plan his method of delivery.

We have enumerated the results and value of each method separately. By combining both methods, the positive results of our procedure are certainly enhanced, and the most complete records for study are obtained. We do not expect our method to replace the obstetrician's routine periodic examination, but to be used concomitantly if possible and as a consultation service if necessary, because we feel that the technique is simple, the time consumed in the process insignificant, and the results of indubitable value.

We hope that our combined method will stimulate further study along these lines.

SUMMARY

Forty gravidas were studied routinely in the last two months of pregnancy, to determine the diagnostic significance of the fetal electrocardiogram and the fetal stethogram, separately and simultaneously, in evaluating the presence of a viable fetus. The individual value of each method was enhanced by the combined study.

The fetal stethogram was positive in 100 per cent of the cases, the fetal electrocardiogram in 80 per cent.

The stethogram is helpful in studying the rate, rhythm, and regularity of fetal heart sounds, the systolic and diastolic phases, murmurs, the uterine souffle, and fetal movements. The intensity of fetal heart sounds depends upon the site at which the microphone is applied, and upon maternal and fetal conditions. In most cases the second sound is louder than the first. As a rule, diastole is longer than systole, but in the presence of fetal tachycardia they may become equal.

The electrocardiogram is valuable in the presence of positive tracings. The absolute diagnosis of fetal presentation is made by the fetal electrocardiogram. If the waves are negative, a vertex presentation is present; if positive a breech presentation is present. In the presence of an equal systolic and diastolic phase, the first sound is recognized by its relationship to the R-wave of the fetal electrocardiogram.

The factors involved in negative electrocardiograms are, a nervous mother, a small fetus, maternal tachycardia, and possibly fetal sinus arrhythmia.

The combined tracings give permanent records of documental value. The maternal electrocardiogram is also recorded.

The use of fetal electrocardiography and fetal stethography for routine and consultation purposes is recommended because of the simple procedure involved and the ease with which tracings can be interpreted.

A case of breech presentation with positive tracing in Lead I, and variations in maternal and fetal rate is discussed.

We wish to express our thanks to the Department of Obstetrics for permission to study their cases. We wish to express our appreciation to Dr. Anthony R. Colonna for his technical assistance.

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Petersen, E.: The Results of Operations on the Sympathetic Nervous System for Benign Gynecologic Conditions, Acta. obst. et gynec. Scandinav. **20:** 1, 1940.

The author analyzes his remote results with pelvic sympathectomy performed for benign gynecologic conditions. Of the 7 patients operated upon for dysmenorrhea, 4 were cured, one was given partial relief and 2 had no relief. In 5 cases of chronic parametritis, 2 patients had complete relief, 2 only partial relief, and 1 observed no change. In 53 patients where the operations were performed for microcystic degeneration of the ovaries, the results were not striking but pain was reduced somewhat more effectively than a control group of 42 patients where no operation was performed.

J. P. Greenhill.

HYPERTHYROIDISM AT THE MENOPAUSE

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IN STATES of ill health, the female patient at the climacteric presents a diagnostic problem to the internist, as well as to the surgeon. The question is, are we dealing with an organic disease or simply with a manifestation of the beginning menopause? The symptoms of the menopause are so protean in nature as to mimic almost any type of organic disease, e.g., cardiac, gastrointestinal, pulmonary, cerebral, pelvic, to mention but a few.

In this presentation we wish to stress the close relationship between menopause and the thyroid gland.

Menopause and hyperthyroidism have many leading symptoms in common. They are: increased sweating, irritability and nervousness, palpitation, increased sense of heat, etc. To differentiate the hyperthyroid symptoms from those of menopause may become very perplexing.

Claiborne[1] in discussing the differential diagnosis of borderline hyperthyroidism has recently commented on this subject. He states, "During the time of the menopause many women have symptoms which are in part suggestive of hyperthyroidism. These patients begin to note a feeling of warmth, perspire readily, are emotionally unstable, cry easily, are irritable, complain of palpitation, and so forth. The decrease in menstruation may confuse the issue: is it a symptom of hyperthyroidism or beginning of the menopause? There is usually no weight loss and no appetite change. An elevated basal metabolic rate is frequently obtained; but repetition gives a drop to normal." It has been our experience that the majority of women at the menopause show a variable basal metabolic rate. According to some investigators, there is a slight fall in the basal metabolism in artificial menopause induced by surgery or roentgen ray castration.[2]

The physiologic relationship between the thyroid gland and the reproductive function is vast and intriguing. Comparatively little factual knowledge on the subject is on hand.

It is a well-recognized clinical fact that thyroid diseases occur more commonly in women than in men; and that the thyroid gland is enlarged at puberty, pregnancy, lactation, and the menopause. The physiologic basis for these clinical observations may be gleaned from the experimental work on the effect of the pituitary on the ovary and the thyroid.

EXPERIMENTAL WORK

Castration in animals increases not only the production of prolan A but also of the thyrotropic factor of the anterior pituitary lobe.[3] The overproduction of the thyrotropic substances result in hyperplasia of the parenchyma of the thyroid

gland with increased vascularization and reduction in the colloid, a histologic picture which characterizes hyperthyroidism.[4] Grumbrecht[5] succeeded in obtaining similar histologic changes in thyroid glands of rabbits when injected with urine from women at the climacteric. It is interesting to note that the thyrotropic substance is found in small quantities in the urine in premature or late menopause, or at the time of comparatively few vasomotor symptoms. On the other hand, the level of thyrotropic substance in the urine is at its peak when the vasomotor symptoms are at their height.[5]

The experimental work of Sherwood and his associates[6] is cogent in this connection. They found a definite decrease in the basal metabolism of adult ovariectomized rats following the administration of estrogen. Estrogen likewise proved effective in reducing the basal metabolic rate of experimental hyperthyroid animals that were not ovariectomized.[7]

From these observations and those of Gessler,[8] the thought comes to mind that perhaps the use of the female sex hormone (estrogen) in thyrotoxicosis at the menopause may prove beneficial.

THE CLINICAL PROBLEM

The problem involved in the diagnosis of the menopause when a nodular goiter is present is far from simple. The emotional instability, sweats, flushes, and the vasomotor symptoms of menopause may mimic those of hyperthyroidism. Needless thyroid surgery is frequently being performed in this group of patients. A recent follow-up study of 100 patients who were advised to have a thyroidectomy for hyperthyroidism revealed that in 15 patients the diagnosis of hyperthyroidism had to be reversed in favor of the menopause.[9] The basal metabolic rate determination cannot always be depended upon for differential diagnosis. Due to the patient's state of apprehension, it is difficult or impossible for her to relax; in the effort to abolish movements, she increases energy expenditure which may cause an increase in metabolic rate. A fleeting emotional upset or a wave of nausea may also increase the metabolic rate.[10]

Since estrogenic therapy is known to control the vasomotor phenomena of menopause, this form of therapy may be employed in the borderline patient before thyroidectomy is decided upon. Recently Davis[11] reported favorable results in the relief of menopausal symptoms in 93 of 100 women by the oral use of stilbestrol. This oral method of administration would appear to offer an additional practical means of differentiating the borderline hyperthyroid patient from menopause.

The following six patients observed at the Temple University Hospital are illustrative of the points under the present discussion.

CASE 1.—E. H., aged 45 years, white, single, was first seen in the Endocrine Clinic of Temple University Hospital on June 6, 1935. Her chief complaint was "nervous indigestion and insomnia." The patient had been suffering with dyspepsia for many years. She had been studied in the gastric clinic; however, no definite etiology had been ascertained. She had lost 10 pounds in the past year. Her menses started at the age of 14 years, were regular, every twenty-four to twenty-six days, lasted three to four days. No pain. Lately they were becoming more scant. Her past medical history revealed that she had an attack of "indigestion" two years ago for which she was confined to bed for six weeks.

Examination showed a thin, middle-aged, white female with a quizzical expression (due probably to her difficulty in hearing); weight was 102½ pounds, height 61½ inches. Temperature was 98° F., pulse 80, respiration 20, blood pressure 140/90. The skin was dry and showed dermatographia. The eyes showed no

exophthalmus. The right lobe of the thyroid was the seat of a nodule, the size of an English walnut. The examination of the heart showed no heart disease. The lungs were clear. There was some tenseness in the right lower quadrant of the abdominal wall. The hair distribution was essentially feminine in type with scant axillary hair. The palms of the hands were moist and cold. The fingers showed no tremor. On June 13, 1935, the basal metabolic rate was minus 9 and the blood cholesterol 240 mg. per 100 c.c. Patient was given ¼ gr. of desiccated thyroid three times daily for two weeks. The pulse rate increased to 128, and the temperature was 99.4° F. The thyroid medication was omitted; however, the pulse rate remained elevated at about 120 per minute for a period of four weeks; during this time she complained mostly of belching. Because of the increased pulse rate and elevated temperature, pulmonary pathology was considered. Physical examination of the chest including roentgenographic studies were negative. No apparent cause for the tachycardia could be found, except for the presence of the adenoma of the thyroid gland. Because of a similar previous experience[12] in which thyroidectomy brought about complete relief from tachycardia and cardiac arrhythmia, the patient was admitted to Temple University Hospital for thyroidectomy. The basal metabolic rate at this time was plus 9 per cent. The cardiologist's report was mild myocardial degeneration secondary to arteriosclerosis and possibly thyrotoxicosis. After proper preparations with Lugol's solution and rest, the patient was operated upon on Sept. 30, 1935. At operation, an adenoma of the right thyroid lobe, the size of a plum, was removed. The left lobe was not disturbed. The microscopic examination of the removed tissue showed numerous large focal regions of fibrous tissue. The thyroid gland itself was inactive. The glands were small and exhibited a moderate amount of mucoid degeneration. Patient was discharged from the hospital on Oct. 7, 1935. For the following two months her pulse rate averaged 88 per minute. The basal metabolic rate was minus 6 per cent, the blood cholesterol 230 mg. per 100 c.c. of blood. On Dec. 17, 1935, she was seen in the Endocrine Clinic with a pulse rate at rest of 100 per minute. Despite sedatives, it continued to vary between 100 and 112 per minute. The patient did not return to our clinic for one year. On Feb. 3, 1937, she came to the clinic complaining of belching, weakness, hot flushes, and vertigo. Her pulse rate was 100 per minute. Her menses were becoming irregular in addition to being scanty. On Feb. 5, 1937, she was started on 2000 rat units of progynon twice a week. After several weeks' treatment, her symptoms began to improve. On April 30, 1937, her pulse rate was 84 per minute, and she weighed 112 pounds (ten pounds more than at first visit) and she had no complaints. Progynon was continued for six months at less frequent intervals than in the beginning of the treatment. When she was last seen at our clinic on Dec. 29, 1937, her pulse rate averaged 84 per minute. Blood pressure was 126/72. Weight 111½ pounds. She had been free of her symptoms and had been able to attend to her household duties.

Comment.—This patient was at the menopausal age (45 years); she had been noting the change in amount of her menstrual flow; she had symptoms of dyspepsia. She also complained of nervousness and insomnia. Her pulse rate was persistently elevated. All of these symptoms could have been due to the oncoming climacteric. Because there were no clear-cut signs of the menopause, such as hot flushes, sweats, vertigo, amenorrhea, this phase of her illness was probably minimized. It is interesting to note that the basal metabolic rate was not abnormal before or after the operation. It is apparent that the primary purpose of the operation, i.e., the relief of the so-called mild thyrotoxic symptoms had not been accomplished. The vasomotor symptoms were not relieved until estrogen therapy was resorted to. A subtotal thyroidectomy in cases of this type may lead to postoperative myxedema as illustrated by the following patient.

CASE 2.—R. H., aged 42 years, white, married, came to the Endocrine Clinic of the Temple University Hospital on Jan. 27, 1937, because of the presence of a "goiter." She had noticed the goiter one and one-half years previously. It had increased slightly in size since then. In addition she complained of nervousness, irritability, easy fatigability, and free perspiration. The menstrual flow was

becoming scant. Her family physician diagnosed her condition as that of toxic goiter. X-ray treatment to the thyroid gland was given for six months. The menstrual flow increased to a more normal amount, but the vasomotor symptoms were unrelieved. When she was told by her doctor that the goiter would have to be removed surgically, she left his care and went to a chiropractor, who treated her for one year with no improvement. At no time had a basal metabolic rate been determined. When she came to the Endocrine Clinic of Temple University Hospital, she still had all of the above symptoms. Her appetite was good and there had been little change in her weight. She also complained of frequent indigestion, epigastric pressure and distention. The physical examination revealed an apprehensive, middle-aged white female, whose face was quite flushed. She was of normal build; her weight was 149 pounds. Temperature, pulse, respiration were 98.2°, 80, 20, respectively. Blood pressure 110/88. There were no eye signs of hyperthyroidism. The pupils were equal and reacted normally to light and accommodation. The thyroid gland was palpable, symmetrically larger than normal, containing a nodule, the size of a walnut in the left lobe. The skin of the upper chest showed the collar flush, characteristic of vasomotor instability. The heart and lungs were essentially normal. There was slight epigastric tenderness on palpation. Other physical findings were essentially normal. Her basal metabolic rate on Jan. 30, 1937, was minus 12 per cent. Our impression was that the patient had a nontoxic goiter and gall bladder disease. She was referred for gastrointestinal studies. Gastric analysis revealed hypoacidity Grade II; gastroscopic examination showed evidence of an atrophic gastritis. X-rays of the gastrointestinal and biliary tracts were negative. The urinalysis was normal, and the blood count was as follows: hemoglobin 8.5 Gm., or 53.5 per cent; red blood cells, 3,950,000; white blood cells, 8,950; color index, 0.69; polymorphonuclears 59 per cent, lymphocytes 37 per cent, and monocytes 4 per cent. The red blood cells showed anisocytosis, poikilocytosis, and achromia. This type of anemia is not infrequently seen at the menopause. The Wassermann test of the blood was negative. The patient was treated for the next three months with iron sulfate, hydrochloric acid, sedatives, and antispasmodics. The blood picture improved considerably, but the gastrointestinal and vasomotor symptoms remained unchanged. In addition, she developed a sensation of tightness in the neck that became quite annoying. The basal metabolic rate at this time was plus 12 per cent. A surgical opinion was in favor of thyroidectomy. On Aug. 11, 1937, a subtotal thyroidectomy was done. The surgeon noted that "the thyroid gland was vascular, hemostasis difficult, vessels sclerosed from previous irradiation." The pathologic report showed that the acini varied greatly in size and shape. All were fairly well filled with colloid and lined by low cuboidal epithelium. There were large areas of the stroma which showed a marked degree of hyalinization. In one section there was considerable hemorrhage. *Diagnosis:* Cystadenoma of thyroid.

The patient made an uneventful recovery and was discharged from the hospital in good condition. Two months after the operation, on Oct. 11, 1937, she came to the Endocrine Clinic complaining of feeling weak and tired. She had occasional swelling of her feet and puffiness about lower eyelids. The pulse rate was 78 per minute. The basal metabolic rate was minus 39 per cent. She was placed on ½ gr. of desiccated thyroid, three times daily, and the dosage was gradually increased to 3 gr. daily. The edema subsided but the vasomotor symptoms persisted. Because of this and scanty menses, she was started on 2,000 rat units of progynon, twice a week. After several weeks she showed improvement. Her flushes, sweating, nervousness, fatigue, all decreased markedly. It is interesting to note that with the rise of the basal metabolic rate, the vasomotor symptoms would increase. On omission of thyroid therapy and administration of progynon, the vasomotor symptoms would subside; however, the basal metabolic rate would decline rapidly and the symptoms of myxedema would become manifest. After the trial and error method, the patient was given ¼ gr. of desiccated thyroid, three times daily and 2,000 rat units of estrogen, once weekly; 3 gr. of iron sulfate, three times daily and 15 minims of hydrochloric acid with each meal. On this regimen she remained free of symptoms and was well maintained. It is worthy of note that when

questioned about the sensation of tightness in her neck, she volunteered the information that she still feels it and sometimes more than before the operation.

Comments.—Here we have another patient at the climacteric with a multitude of bizarre symptoms suggestive of adenoma of the thyroid gland, gall bladder disease, pernicious anemia, and menopause. Such patients are often easier to pigeonhole diagnostically after failure in therapy than before treatment. The original symptoms of scanty menses, nervousness, vasomotor signs, etc., could have been due to early climacteric. The gastrointestinal symptoms were those of hypochlorhydric hypochromic anemia of menopause. It is unfortunate that the patient fixed her attention on her "goiter" and "tightness" in the neck. The fixation was so marked as to lead her medical attendants to believe that the thyroid was conditioning her symptoms to the exclusion of a physiologic process of menopause. There is a strong possibility that the thyroid which was removed was already hypofunctioning, and the adenoma had undergone cystic degeneration. The surgical removal of the thyroid not only failed to cure the patient's symptoms but aggravated her condition by bringing about a myxedematous state.

On the basis of the experience with these two cases, we treated the following two patients' similar symptoms by medical measures rather than by surgical intervention. The progress of these cases is as follows:

CASE 3.—A. McN., aged 45 years, white, married, was referred to the Endocrine Clinic of Temple University Hospital on Sept. 14, 1937, for a basal metabolic rate determination, and physical examination prior to an operation for a toxic adenoma of the thyroid gland. The essential findings in our clinic were as follows: A history of easy fatigability, excessive sweating, and frequent attacks of palpitation. There had been no weight loss. There had been an artificial menopause at the age of 30 years, following hysterectomy for fibroids, but no vasomotor symptoms developed until four years ago. Past medical history was irrelevant. Examination revealed a middle-aged woman, weighing 149 pounds and of average build. The face was flushed; the skin of body was moist and of normal texture. The neck showed a small nodule the size of an olive in the isthmus of the thyroid gland. The palms of the hands were moist and the extended fingers showed a tremor. The heart rate was slightly elevated, apical rate 96, no murmurs and no arrhythmia. The lungs were clear. The other findings were within normal limits. A basal metabolic rate on Sept. 17, 1937, was plus 37 per cent. Despite the elevated basal metabolic rate, she was considered to suffer from menopausal symptoms. She was given one international unit of progestin, three times a week. After six injections, she stated that she was less nervous, felt much improved, and her pulse rate declined to 80 per minute. A basal metabolic rate determination on Oct. 21, 1937, was minus 6 per cent. Unfortunately a blood cholesterol was not determined due to clotting of the blood specimen in the tube. The patient received 16 more injections of progestin. She was free of symptoms and when we last heard from her, she was reported to be in good physical condition and not taking any medication.

Comment.—This case discloses a few pertinent points. First, the elevated basal metabolic rate (plus 37) may have been due largely to the patient's fear of surgery. DuBois has mentioned this as an important factor in false readings of basal metabolic rates. It is imprudent to say to the patient, "We'll do a basal metabolic rate to see whether your thyroid will have to be removed surgically." Second, the drop in basal metabolic rate from plus 37 to minus 6 may, therefore, be due to improvement of vasomotor symptoms. Be that as it may, the relief of the patient's symptoms following the injections of progestin is highly suggestive that we were not dealing with a true toxic goiter, but rather with vasomotor phenomena of menopause.

CASE 4.—J. I., aged 43 years, white, married, was referred to the Endocrine Clinic of Temple University Hospital by her family doctor with a note that she had had for many years a simple goiter, asymptomatic. Two months ago she had bronchopneumonia. During the course of that disease symptoms of an exophthalmic goiter became manifest. The findings at our clinic were as follows: Patient noticed a "lumpy swelling" over anterior region of neck about three years ago. This lump was stationery in size until September, 1938, at which time she devel-

oped bronchopneumonia. Soon after this the mass increased in size. She tired easily; had palpitation and dyspnea on exertion. Menstrual history: onset at 11 years, regular until the age of 20 years; after this the menses became scanty, lasting two and one-half days; no dysmenorrhea. After the age of 20 years, her menses were irregular with occasional long intervals of amenorrhea. At 41 years, her menses became regular at every twenty-eight days, but quite scant. At that time vasomotor symptoms developed, particularly frequent hot flushes.

Physical Examination.—Weight was 192 pounds; temperature, 98.3° F., pulse, 88; respiration, 28; blood pressure, 140/80. Patient was an obese, phlegmatic white female who did not appear acutely ill. The skin of the body was dry and warm with marked dermatographia. The palms of the hands were moist and warm. There was no tremor of the hands. The eyeballs exhibited a luster. The pupils were equal and regular and reacted promptly to light. There was no widening of palpebral fissure, exophthalmus or lid lag. The face was flushed; the tongue was slightly coated; the tonsils were large and swollen. The right lobe of the thyroid was about the size of a hen's egg, smooth in outline, and semisolid in consistency. The left lobe and isthmus were also enlarged but about one-third that of the right side. They had the same consistency as the right lobe. Chest examination revealed decreased resonance in right subscapular region and many crepitant rales in the middle lobe of the right side. Similar rales were audible in the corresponding area on the left side. There was no heart disease. The abdomen was negative. Neurologic examination showed no central nerve lesion.

Laboratory Findings.—Basal metabolic rate was plus 21 per cent. The x-ray of the chest showed no pulmonary tuberculosis but evidence of bronchiectasis. Patient was given Lugol's solution gtt. X three times daily for ten days and the basal metabolic rate was plus 11 per cent. A recheck one week later showed no further change in the basal metabolic rate. Despite the lowering of the basal metabolic rate from 21 to 11 per cent after taking iodine solution, we felt that the patient was not suffering from hyperthyroidism, but rather presented symptoms of menopause complicated by a bronchiectasis. We gave her estrogenic therapy consisting of 2,000 rat units of estrogen, twice a week. After twelve injections (six weeks), she stated that she felt much better and was free of vasomotor symptoms. Estrogenic therapy was continued. One month later her pulse rate was 68 per minute; the flushes were less frequent and less intense. For her pulmonary pathology she was referred to the chest clinic. When estrogen was omitted during the month of June, 1939, the vasomotor and nervous symptoms recurred within three weeks. Resumption of treatment with estrogen cleared her of these symptoms.

Comments.—We were dealing with a patient at the menopausal age who noticed an enlargement of the thyroid three years ago. The goiter apparently enlarged following a bronchopneumonia. A survey of the menstrual history showed that two years previously her menses were becoming scant and vasomotor symptoms became manifest. Despite the fact that her basal metabolic rate was plus 21 per cent, we felt that there was no emergency and a trial with estrogen would be indicated. Estrogen relieved her vasomotor symptoms which in the presence of an elevated basal metabolic rate were suggestive of thyrotoxicosis. This patient was thus spared the risk of an unnecessary thyroidectomy.

CASE 5.—Mrs. K. F., white, aged 47 years, was admitted to Temple University Hospital, Sept. 14, 1939, for thyroidectomy. Ten years ago she first learned that she had hypertension on being examined for life insurance; six years ago she had a blood Wassermann test which proved strongly positive, for which she received 7 intramuscular injections of bismuth salicylate. She failed to return for further treatment until the fall of 1939. Her blood Wassermann test was still strongly positive and her blood pressure was 240/136. Antisyphilitic treatment was started again; however, she continued to complain of nervousness, irritability, easy fatigability, and loss of weight, having lost 34 pounds in the past several months. She also suffered from pain over the precordium that radiated down the left arm. Patient has had an enlarged thyroid gland since the age of eleven years which in the past fifteen years grew larger; however, there has been no pain referable to the thyroid gland, no difficulty of swallowing or choking sensation. Menstruation com-

menced at the age of 13 years, was always regular and of normal flow; in the past seven months, the intervals were less frequent and the flow less scant.

On admission to the Hospital, the patient appeared underweight, very alert, and quite cooperative. There was capillary flushing over neck and upper chest. The thyroid gland was enlarged; the right lobe and isthmus contained firm nodules; the left lobe was diffusely enlarged. The outstretched fingers of both hands showed no tremor. The lungs were clear. The heart was markedly enlarged to the left. There was a diastolic murmur audible at the apex and systolic and diastolic murmur were heard at the base. The pulse was 90 per minute, quickly receding; the blood pressure was 175 systolic and 95 diastolic. The liver and spleen were not palpable. The deep tendon reflexes were present and active; there was no clonus and no Babinski. Romberg was negative. There was no weakness of the quadriceps femoris muscle group.

Laboratory Findings.—Basal metabolic rate plus 32 and plus 37 (after five days of Lugol's solution). Blood Wassermann reaction was four-plus. Spinal fluid was negative for Wassermann test and colloidal gold. Urea nitrogen was 14 mg. per 100 c.c. of blood, and urea clearance 56 per cent of normal, first hour and 72 per cent second hour. Blood count: hemoglobin, 10 Gm.; red blood cells, 4,000,000; white blood cells, 8,300; polymorphonuclears, 83 per cent; small lymphocytes, 16 per cent; large lymphocytes, 1 per cent. X-ray of the chest showed enlarged heart, and widening of root of aorta. Both exhibited abnormal and vigorous pulsations, and the arch of the aorta was not aneurysmal. The lung fields were clear; there was old adhesive pleurisy at both costodiaphragmatic angles. Patient was seen by various men of the staff of Temple University Hospital, and it was the general consensus of opinion that she should not be operated upon, as she probably did not suffer from thyrotoxicosis. She was given antisyphilitic treatment; however, she continued to complain of nausea, hot flashes, vertigo, and palpitation. She developed menorrhagia for one month. It was the opinion of the gynecologic clinic that the patient was undergoing the menopause. After cessation of bleeding she was given 2,000 rat units of estrogen, twice weekly for a period of several months. She was last seen in the medical clinic on July 8, 1940; patient had improved considerably, having an occasional hot flush, but no nausea, no palpitation, and no irritability. She is still attending the clinic for antisyphilitic treatment.

Comment.—The evaluation of the clinical signs and laboratory findings in this patient presented some difficulty: That she had syphilitic heart disease and hypertension was quite evident. It is true that in hypertension there may be loss of weight and elevated basal metabolic rate. Wohl and Robertson[13] found an elevated basal metabolic rate of plus 27 per cent in hypertension. However, the presence of nodules in the right lobe of the thyroid and enlargement of the left lobe suggested the possibility of thyrotoxicosis. The failure of iodine administration to relieve the clinical symptoms and to reduce the basal metabolic rate spoke against the existence of thyrotoxicosis. The symptoms of vasomotor instability were doubtless due to menopause. Similar symptoms, however, may be obtained in hypertension. However, upon administration of estrogen, the vasomotor symptoms cleared in spite of the fact that the blood pressure remained high.

CASE 6.—Mrs. M. F., aged 41 years, was admitted to the hospital on May 13, 1933, with complaints of nervousness, flushing, and extreme palpitation. She had been treated for nervousness by a physician about three years prior to admission, although she had an enlarged thyroid gland at that time. Her symptoms failed to respond to treatment. In November, 1932, she had a tonsillectomy, followed by vaccine therapy. Shortly thereafter, her nervousness increased and she developed palpitation, easy fatigability, and flushing. The menstrual history was essentially normal and regular; however in the past four months the flow was scant. Physical examination revealed a well-nourished white female, who was quite apprehensive. The eyes "had a stare" with suggestion of a positive von Graefe sign. The thyroid gland was enlarged and rather firm. There was marked pulsation of the vessels of the neck. The heart was enlarged especially to the left; first sound, forcible and loud. There was a reduplication of the second sound. Blood pressure was 160/70, and pulse 110. *Abdomen:* No intra-abdominal masses were felt. *Extremities:*

There was a fine tremor of the outstretched fingers of both hands. There was weakness of the quadriceps femoris muscle group. *Laboratory Findings:* Basal metabolic rate plus 35 per cent. After bed rest, sedatives, and iodine administration, patient had a subtotal thyroidectomy by Dr. W. Wayne Babcock. She had a stormy convalescence during which time the pulse rate increased to 160. However, she left the hospital considerably improved ten days after the operation. The histologic examination of the thyroid gland by Dr. Frank W. Konzelmann showed it to be a hyperplastic thyroid of the toxic type. Patient returned three months later after thyroidectomy. She gained weight, had less frequent attacks of palpitation and tired less readily; however, her nervousness and flushes continued. Pulse rate was 82. The blood pressure was 150/90. Menstruation became irregular, lasting only one day. She was placed on estrogen therapy, 2,000 rat units weekly and sedatives. After three months of this therapy, her nervousness decreased; the flushes ceased, and she was able to resume her household duties.

Comment.—This case represents a combination of manifestations of thyrotoxicosis and that of menopause. Although the operation cleared many of the symptoms, patient was not restored to complete health until her menopausal symptoms were attended to.

SUMMARY AND CONCLUSIONS

We have endeavored to correlate vasomotor symptoms of menopause with functional disturbances of the thyroid and pituitary glands. A patient at the menopausal age may suffer with hyperthyroidism alone, without having any true climacteric symptoms. More often, however, the vasomotor phenomena may mislead the clinician by simulating hyperthyroidism. The basal metabolic rate, particularly as a criterion for thyrotoxicosis, may lead one astray at the menopause. The result is often needless surgery. When such a patient is operated upon, the menopausal symptoms are not relieved, and the patient is exposed to the danger of developing postoperative myxedema. Thyroidectomy is rarely an emergency operation. Therefore, in borderline cases, before thyroidectomy is performed, the patient should be given the benefit of medical treatment, particularly estrogenic therapy. Stilbestrol may prove to be the simplest procedure.

These six cases are reported to illustrate the difficulties in diagnosis and management of borderline hyperthyroidism at the menopause. Three patients who had thyroidectomy failed to improve until estrogenic therapy was instituted. One of this group developed postoperative myxedema which complicated therapy. In three cases thyroidectomy was withheld and estrogenic therapy brought about complete amelioration of vasomotor symptoms.

We are indebted to the various members of the Medical and Surgical Staffs of Temple University Hospital for their cooperation.

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THE ADVANTAGES OF CONSERVATIVE OBSTETRICS AS SHOWN BY EXAMINATION SIX WEEKS POST PARTUM*

A Review of Two Thousand Cases

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IN CARING for an obstetric patient, the accoucheur's greatest aim is to bring to a successful conclusion one of nature's processes, both from the point of view of the mother and of her baby. There is hardly a doubt in the minds of most of us that the end result of any obstetric case is a reflection of what has gone on not only after delivery, but in very great part what has been done prior to, and more particularly at the time of delivery. After delivery one can only aim to restore the pelvic organs to their physiologic normal condition in a reasonable period of time, usually considered by most obstetricians as six weeks.

The general attitude at the Boston Lying-in Hospital is one of conservatism, and it is because of this that during the past decade we have been able to place not only our morbidity, but the maternal and fetal mortality at the lowest level in the history of the hospital. Our morbidity averages 5.5 per cent.

The results we feel are due in some measure to the judicial use of analgesics in labor. It is apparent from our observation during the past ten years, that patients receiving medication are less likely to be unnecessarily interfered with, whereas in nonmedicated cases, the sympathy for the patient on the part of the doctor too often interferes with the management of normal labor. In other words, we give the natural forces of labor every opportunity to play a great part in the management of the obstetric case.

Manual dilatation in our opinion is an extremely serious procedure, both from the maternal and fetal standpoints. There were no patients in our series in whom the cervix was manually dilated; in fact, in the past five years in this hospital no cervix has been manually dilated. Williams,[1] Parker,[2] and Crist[3] emphasize this principle in insisting on no manual dilatation of the cervix. To quote the latter: "There is no such thing as manual dilatation. Where such is attempted it results in manual separation or manual laceration." Blair[4] very beautifully expresses his appreciation of the cervix when he says, "I cannot remember as an undergraduate that very much emphasis was placed on the cervix uteri. I think little attempt is made to give the undergraduate that attitude of respect, almost reverence, that is so necessary to treatment."

Too often inertia is considered an indication for manual dilatation. We prefer to treat this condition more conservatively. In some cases

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where the cervix is not taken up, sedation is best; in others fairly well advanced in labor, it is best treated by stimulation. If the cervix is partially dilated and effaced, simple rupture of the membranes often advances labor satisfactorily; small amounts of pituitary extract, namely in one minim doses, when not contraindicated, are a valuable adjunct, certainly far more so than attempted manual dilatation.

It is our policy to deliver as many patients as possible normally or by low forceps. High forceps have been abolished. Internal podalic version has only a rare indication. Midforceps are but seldom necessary. Breech extractions are fast disappearing because of the policy of practicing external version after seven months. We allow two hours in the second stage without progress, at which time an episiotomy, preferably a median one, is made, and when possible the baby is delivered normally with the aid of superfundic pressure. If this fails, low forceps are applied. Other than maternal and fetal distress there are only two usual indications for forceps extraction at full dilatation, namely, prematurity and patients with organic heart disease. DeLee[5] advocates for the specialist what he terms prophylactic forceps. On the other hand, Greenhill[6] advocates at least one hour in the second stage without progress. As noticed in Table I, 64 per cent of our series were delivered normally and 25.85 per cent by low forceps. Four per cent of the remaining were delivered by cesarean section. The use of the latter in cases of suspected cephalopelvic disproportion has been governed by successive lateral Thom's x-rays. We feel that this conservatism contributes considerably to more satisfactory end results.

TABLE I. METHOD OF DELIVERY

	NORMAL DELIVERY	PRIMIP. LOW FORCEPS	MULTIP. LOW FORCEPS	ABORTION	BREECH	MULTIPLE PREGNANCY	CESAREAN SECTION	VERSION	BRAXTON HICKS VERSION	MID-FORCEPS
Cases	1280	471	46	22	41	24	80	8	11	17
Per cent	64	23.55	2.3	1.1	2.05	1.2	4	0.4	0.55	0.85

As will be noted later (Table VI), 86.5 per cent had a satisfactory end result at six weeks. We attribute this to a lack of manual interference during labor plus routine post-partum care which our patients have received for some time. This routine begins with having our patients in a semisitting position soon after delivery, encouraging the patient to move from side to side frequently, and the beginning of exercises on the third day post-partum, all of which, we feel, aid involution. Ergot is not given routinely, but in patients who show evidence of subinvolution one drachm of fluid extract of ergot is given t.i.d. for three days. Patients still showing evidence of subinvolution on the tenth day are then started on two-gallon sterile douches at 110° F. Marked improvement is usually immediately noticed. Normal patients are allowed up on the tenth day and discharged on the fourteenth day. Patients

who have had a cesarean section are allowed up on the fourteenth day and are discharged on the seventeenth day. Patients are advised not to climb stairs for at least a week after discharge, and for a period of three weeks after discharge they are encouraged to have bidaily rest periods. The improvement in patients with subinvolution receiving hot vaginal douches, coupled with the findings at six weeks' post partum of many patients with moderate degrees of subinvolution, and eroded and edematous cervices, led us to the policy of instructing all patients to start douches on leaving the hospital, continuing them until their six weeks' return visit. If, on discharge examination, a patient is found to have a retroversion, she is further instructed to take knee-chest exercises. These instructions are distributed to each patient on a typewritten sheet, so there may be no doubt in the mind of the patient as to what she is to do.

To note our end results statistically we studied the records of 2,000 consecutive admissions. Parity and age distribution are shown in Tables II and III.

TABLE II. PARITY DISTRIBUTION

	i	ii	iii	iv	v	vi	vii	viii	ix	x+
Cases	1224	383	152	104	53	36	25	9	7	7
Per cent	61.2	19.15	7.6	5.2	2.65	1.8	1.25	0.45	0.35	0.35

TABLE III. AGE DISTRIBUTION

	UNDER 20	20-24	25-29	30-34	35-39	40+
Cases	160	731	582	320	163	44
Per cent	8	36.55	29.1	16	8.15	2.2

Much variation in the treatment of the perineum is discussed in the literature.

Potter[7] advises against episiotomy but prefers to iron out the perineum with green soap, believing that this prevents shock, and that the elasticity of the muscle is not destroyed. Danforth,[8] Greenhill,[6] Kelley,[9] Sellers and Sanders[10] advise routine episiotomy. Cooke[11] favors median episiotomy, but states neither is necessary in 10 per cent of primiparas. Lubin[12] prefers episiotomy to laceration but states that 50 per cent of all deliveries have an intact perineum. We believe this statement may be true but the levators beneath the mucous membrane are undoubtedly separated in a large percentage of these cases, resulting in a relaxed pelvic floor. Routine episiotomy will protect the patient in later years from the necessity of perineal repair. The incision of the perineum in the median raphe seems to be ideal. Michaelis first described this in 1799. In our series, 40.8 per cent had median against 17.7 per cent of mediolateral episiotomies. The remaining 41.5 per cent are comprised of lacerations and intact perinea. To us this latter percentage seems high as compared to that in private practice. This percentage of lacerations and intact perinea is due to two causes: first, a good number of these patients are delivered by externs at home where routine episiotomy is not practiced for obvious reasons; and second, many of these patients were previously not treated with an episiotomy and started out with a relaxed perineum. The median episiotomy has the advantage over all others in that it heals more readily, causes much less discomfort, and anatomically is a mere separation of the levators rather than a severing of their fibers. Cooke[11] agrees with the above principle, because he also believes severed transverse muscle bundles do not heal as readily as simple separation of the levators. At this hospital we advocate routine median episiotomies unless contraindicated.

TABLE IV. TREATMENT OF PERINEUM AT DELIVERY

	LACERATION FIRST DEGREE	LACERATION SECOND DEGREE	LACERATION THIRD DEGREE	MEDIAN EPISIOTOMY	MEDIO-LATERAL EPISIOTOMY	INTACT
Cases	44	43	5	816	354	741
Per cent	2.2	2.15	0.25	40.8	17.7	37.05

It will be noted in Table V that there is a very low percentage of poor results in perineal support. The preparation prior to delivery, we believe, has not too little influence on this fact. The routine use of enemas at the onset of labor, thoroughly emptying the lower bowel, abolishes certain risk of infection by eliminating the expression of feces over the perineum as the head descends in the pelvis. Furthermore, the use of the lithotomy position for delivery with the lower end of the table dropped aids toward keeping a sterile field, as well as allowing for an excellent exposure.

TABLE V. CONDITION OF PERINEUM AT SIX WEEKS' EXAMINATION

	HEALED AND GOOD SUPPORT	HEALED AND MODERATE SUPPORT	MODERATELY RELAXED	MARKEDLY RELAXED WITH CYSTOCELE AND RECTOCELE	PERINEAL FISTULAS	RECTO-VAGINAL FISTULAS
Cases	1694	108	144	46	8	2
Per cent	84.7	5.4	7.2	2.3	0.4	0.1

Intermediate repairs of old relaxed perinea are advocated by Tracy,[13] Crist,[3] Gayden and Plass,[14] Hanna,[15] Pride,[16] and Kelley.[9] It has not been the policy of the Boston Lying-in Hospital to routinely follow such procedure, because there are new interns entering the service each month. It is the private opinion of the authors that in cases of relaxation of the perineum a reasonably satisfactory result may be obtained by such a procedure. The result, however, is not considered as being as satisfactory as if the patient had had repeated episiotomies or gynecoplastic repair after the childbearing age.

Conservatism is also the rule in treatment of the cervix. We do not inspect cervices at the time of delivery, nor do we advocate immediate suturing of the cervix except when there is hemorrhage. We definitely feel that the cervix should be inspected only in certain cases, even in the absence of hemorrhage, namely, patients with old cervical repairs, previous cesarean section, breech extraction, internal podalic version, and in cases where there has been manual dilatation. As previously stated, the latter three occur with great infrequency in our hospital. In our 2,000 cases, it was found necessary to suture the cervix in 23 cases, only one and one-tenth of one per cent. It may be stated here that of these 23 cases, only one received pituitrin before the cervix was fully dilated, and in this case, only one minim was given for inertia when the cervix was four-fingers dilated. Further, in these 23 patients, 7 were febrile, a morbidity of 30 per cent, practically six times higher than the morbidity of the entire group, which averaged 5.5 per cent. This morbidity is not a corrected one and is based on any patient with

a temperature of 100.4° F. or over on two consecutive days, regardless of cause or time in the puerperium. Our end results, we believe, are good evidence in favor of the pursuance of these conservative policies. As noted in Table VI, 68.3 per cent of our patients at six weeks had a completely healed cervix, 18.2 per cent had a very slight circumoral erosion with no eversion or laceration. Most of these latter would ordinarily be considered within normal limits. Thus 86.5 per cent of our patients at six weeks postpartum had a satisfactorily healed cervix. As a corollary to this, Table VII shows that at six weeks 90.75 per cent of our patients had either no leucorrhea or insufficient to necessitate the use of a perineal pad.

TABLE VI. CONDITION OF CERVIX AT SIX WEEKS' EXAMINATION

	HEALED AND NO EROSION	CIRCUMORAL EROSION	EROSION ANTERIOR LIP WITH EVERSION	MODERATE EROSION BOTH LIPS WITH EVERSION	DEEP BILATERAL LACERATION	UNILATERAL LACERATION	STELLATE	ENDOCERVICITIS	BOGGY
Cases	1366	364	52	163	14	3	20	23	4
Per cent	68.3	18.2	2.6	8.15	0.7	0.15	1	1.15	0.2

TABLE VII. PRESENCE OF LEUCORRHEA SIX WEEKS POST PARTUM

	NONE	SLIGHT BUT NO PAD	MODERATE NO PAD	MODERATE WITH PAD	PROFUSE
Cases	1235	580	58	124	3
Per cent	61.75	29	2.9	6.2	0.15

As far as is possible, a fairly definite routine is followed in the treatment of the cervix at six weeks. If there is a small circumoral erosion, the vagina and the cervix are wiped clean, and 25 per cent silver nitrate is applied to the erosion. The patient is instructed to begin daily douches one week following this treatment and to continue them daily for five weeks when she returns for another check-up. If the erosion has improved, silver nitrate may be applied again. However, if there has been no improvement then the erosion is treated with electrocautery. Instructions following this are the same as that following silver nitrate. The end results of this treatment are shown in Table VIII where it is

TABLE VIII. TREATMENT OF CERVIX AT EXAMINATION SIX WEEKS POST PARTUM

	NONE	SILVER NITRATE	CAUTERY	SILVER NITRATE PLUS CAUTERY	SILVER NITRATE TWO TIMES PLUS	CAUTERY TWICE	CAUTERY THREE TIMES PLUS
Cases	1381	303	126	101	30	36	2
Per cent	69.05	15.15	6.3	5.05	1.5	1.8	0.1

noted that 69.05 per cent of our patients required no treatment at six weeks' examination; 15.15 per cent had such a slight erosion that one

treatment with 25 per cent silver nitrate was sufficient to heal the cervix and enable them to be discharged at the next visit. After electrocautery, 6.3 per cent needed no further treatment. In other words, 90.5 per cent of our patients showed a healed cervix at twelve weeks post partum. Further, 5.05 per cent received cautery once following application of silver nitrate. The reason in most cases for this procedure is the policy of never using cautery immediately preceding an impending catamenia. These patients were instructed to return for cautery at the cessation of their menstrual flow.

TABLE IX. RETURN VISITS

	DISCHARGED AT SIX WEEKS	1 VISIT AND DISCHARGED	2 VISITS AND DISCHARGED	3 VISITS AND DISCHARGED	4 VISITS AND DISCHARGED	5 VISITS AND DISCHARGED	6 VISITS AND DISCHARGED	DID NOT RETURN
Cases	1382	373	146	53	21	3	4	160
Per cent	69.1	18.6	7.3	2.65	1.05	0.15	0.2	8

This foregoing routine has further proved more gratifying as evidenced by the fact that 69.1 per cent were discharged at six weeks without any treatment and 18.6 per cent after one subsequent visit, or a total of 87.7 per cent were discharged within a period of twelve weeks post partum.

We, therefore, feel that 25 per cent silver nitrate and the electrocautery are important as valuable adjuncts in the treatment of the postpartum cervix.

Along with cautery, conization of the cervical canal, as described by Hyams[17, 18] for the treatment of chronic cervicitis, is very valuable. General anesthesia is not needed for this procedure. Fifty per cent cocaine in the canal for five minutes is sufficient to give adequate local anesthesia.

The foregoing policies and the resultant figures are not at variance with other authors as noted in a review of the literature of the past ten years.

Goff[19] reviewed the subject historically, noting that it was Sir James Simpson in 1851 who pointed out that cervical lacerations were a frequent occurrence and occasionally unavoidable. This was further described by Robert Ellis of London in 1861. However, it was not until 1874 that Montrose A. Pallen performed immediate suture of the cervix at two weeks. The indications here were also hemorrhage. Then in 1884 Carl Schroeder described his operation. A number of men, Bernstein,[20] Danforth,[8] Emrick,[21] Galloway,[22] Goff,[19] Hanna,[15] Kelley,[9] MacFarlane,[23] McCarley,[24] Miller,[25] Potter,[7] Pride,[16] Sellers and Sanders,[10] and Speidel[26] believe in the immediate repair of the cervix. Potter[7] goes one step further in stating that the cervix after manual dilatation has a much better appearance than that of a cervix not manually dilated. This, of course, is contrary to our opinion. Danforth[8] sutures any laceration of 2 cm. whether or not bleeding is present. He reports 75 per cent of good results. However, C. B. Reed[8] in discussing Danforth's work felt that in many of his cases the cervix was too edematous for immediate suture, and in these cases the sutures cut through. Reed further states that in some cases he has repaired one side and not the other due to edema, and later found the unsutured side healed. Goff[19] reports many figures, some of which seem contrary to his conclusions. His morbidity in repaired cervices is at least twice as great as in his unrepaired cases.

In primiparas with lacerated cervices not repaired, he reports a morbidity of 8.1 per cent as contrasted with 16.1 per cent in the repaired cases; the occurrence of post-partum cervical infections is 6 per cent in primiparas where the lacerated cervix was not repaired, as against 5.4 per cent in primiparas where the cervix was repaired, certainly not an appreciable difference. With these figures, Goff concludes that: "Immediate trachelorrhaphy though the immediate and remote results are not ideal is a valuable prophylactic procedure against post-partum cervical infections and their sequelae." Hanna,[15] admitting that the birth canal is very susceptible to infection and therefore should be treated as a surgical wound, advocates immediate repair of the cervix even in home deliveries. Speidel[26] goes so far as to use forty-day No. 2 chromic catgut. On the other hand, we find that others, such as Cooke,[11] Adair,[27] Hofbauer,[28] and Crist,[3] advocate suture of the cervix only in the presence of hemorrhage. Some authors prefer the intermediate type of repair. Tracy[13] and Williams[1] advise repair five to ten days post partum. Dickinson, as reported by Danforth,[29] repairs at two to three days post partum, and Hirsh and Coffee, as reported by McCarley,[24] repair five and ten days post partum, respectively. We feel that in the light of our present results this is an unnecessary added risk to the patient, for it certainly necessitates a second anesthesia and operation.

Our immediate post-partum treatment has been already outlined in detail above. As was stated previously in this paper, all patients at the time of the thirteen-day examination are advised to take douches daily, regardless of the presence or absence of retroversion. The literature is conspicuous by the absence of discussion in the use of douches post partum. Prior to the routine use of douches we noted that a large percentage of patients at six weeks showed subinvolution and large, boggy, and eroded cervices sufficient to require depletion before cautery could be safely used. This led us to believe that if depletion by douching were started early in the puerperium, any necessary treatment would not be delayed at the six weeks' examination. We were pleased to find in our series a very small percentage of subinvoluted uteri, namely 2.9 per cent. At the six weeks' examination, patients with retrodisplacement were treated in one of several ways. First, those with asymptomatic retroversions were not given any treatment but were told to return should symptoms, such as backache, menorrhagia, or dysmenorrhea, occur. Second, those with a retroversion having any of the above symptoms associated with an enlarged uterus were treated with a Smith Hodge pessary after the uterus had been replaced manually or with the aid of a tenaculum on the cervix. These patients as far as could be controlled wore the pessary for three months, changing it at six-week intervals. The patient was instructed to take daily douches throughout this period and was told to return four to six weeks after the three-month period of wearing the pessary for a final check-up. Many of these patients did not return presumably because of the absence of symptoms. At this subsequent examination, patients who were found to have an anterior uterus were considered as permanently cured, while those who had asymptomatic third-degree retroversions were considered as probably temporarily cured and were instructed to return should symptoms recur. Only patients showing a retroversion with symptoms having been relieved with the pessary were referred for suspension.

Knee-chest exercise is a recognized and practiced method of correcting third-degree retroversions. Unfortunately we are unable to report a

sufficient group who had conscientiously taken knee-chest exercises. However, it is our opinion that knee-chest exercises in themselves do not cure more than a small percentage of third-degree retroversions.

Moses,[30] in a critical study at the Florence Crittenden Home, reports on a controlled series of 210 patients who received no treatment and 210 patients who received knee-chest exercises from the tenth day post partum. At the end of six weeks' post partum, his findings were exactly the same in both groups, namely 64.7 per cent were anterior and 35.2 per cent were posterior.

In evaluating our end results, one notes from Table X that 11.45 per cent of our patients had a third-degree retroversion, and of this group three-fourths, as shown in Table XI, were asymptomatic.

TABLE X. UTERUS AT SIX WEEKS POST PARTUM

	ANTERIOR FREELY MOVABLE, NORMAL SIZE	FIRST DEGREE RETROVERSION, NORMAL SIZE	SECOND DEGREE RETROVERSION, NORMAL SIZE	THIRD DEGREE RETROVERSION, ENLARGED	ANTERIOR AND ENLARGED	PROLAPSED UTERI	TOTAL THIRD-DEGREE RETROVERSION
Cases	1246	178	280	11	47	20	229
Per cent	62.3	8.9	14	.55	2.35	1	11.45

TABLE XI. CLASSIFICATION OF RETROVERSIONS

	TOTAL THIRD-DEGREE RETROVERSIONS	ASYMPTOMATIC	SYMPTOMATIC
Cases	229	177	52
Per cent		77.28	22.72

TABLE XII. TREATMENT OF SYMPTOMATIC THIRD-DEGREE RETROVERSIONS WITH RESULTS

	PESSARY FOR THREE MONTHS	ANTERIOR AFTER TREATMENT WITHOUT SYMPTOMS	ANTERIOR AFTER TREATMENT WITH SYMPTOMS	POSTERIOR AFTER TREATMENT WITHOUT SYMPTOMS	POSTERIOR AFTER TREATMENT WITH SYMPTOMS
Cases	35	20	2	11	2
Per cent		57.1	5.7	31.5	5.7

TABLE XII-A. TREATMENT OF RETROVERSIONS CONTINUED

	PESSARY WORN LESS THAN THREE MONTHS	ANTERIOR AFTER TREATMENT WITHOUT SYMPTOMS	POSTERIOR AFTER TREATMENT WITHOUT SYMPTOMS	POSTERIOR AFTER TREATMENT WITH SYMPTOMS
Cases	17	13	3	1
Per cent		76.4	17.4	5.8

The treatment of the remaining 22.72 per cent of symptomatic cases is shown in Table XII and XII-A; 63.4 per cent of these patients with third-degree retroversions, wearing a pessary for three months or less,

were permanently cured, which compares favorably with figures reported by Cooke[32] and Abbott.[33] 26.8 per cent of these patients had a retroversion after treatment but were asymptomatic. These we considered as relieved though retroversion still persisted. We may, therefore, conclude that 90.2 per cent of the patients with third-degree retroversions treated by pessary were either relieved of their symptoms or permanently cured. There were three patients of this group whose uteri remained retroverted in spite of treatment and were referred for suspension. Two of the total number had an anterior uterus after treatment but continued to have symptoms. These we felt were definitely associated with relaxation of the pelvic girdle. With a high percentage of successful results as noted above, we would like to emphasize the importance of the Smith Hodge pessary not only as a method of treatment but as a diagnostic procedure prior to suspension.

Harris, and associates,[34] in an experimental study of 8 cadavers, found that the upper two-thirds of the paravaginal tissue or the lower two-thirds of parametrial tissue were necessary for uterine support. Section of the round, ovarian, and infundibulopelvic ligaments, plus the upper third of the broad ligaments, had no effect on uterine descent as long as the above-mentioned structures were intact. With this fact in mind it seems logical to believe that depletion douches may strengthen the paravaginal and parametrial tissues.

Parker[2] emphasizes the importance of rest, exercise, little or no step walking, knee-chest position, kangaroo walk, as valuable in aiding a return to normal. He states that normal involution is not complete for twelve weeks and further, that from 18 to 42 per cent of women have retroversion, half of which are symptomless. Cook[32] believes that the knee-chest position and similar exercises, such as the elephant walk, have greatly reduced the number of patients needing a pessary. He believes that 60 to 70 per cent of puerperal retroversions have a permanent cure when the pessary is used at six weeks' post partum. Galloway[22] advocates back rest and face position on third day, wheel chair on sixth, steps on ninth, and discharge on the twelfth. His patients do calisthenics after lochia has disappeared and knee-chest exercises twice a day for ten minutes until six to eight weeks' return. Kanter and Klaman[35] advise, as a preventive for retroversion to give ergot for three days, turn patient from side to side, have her lie on the abdomen, and to sit up on the fifth day on a back rest. Contrary to the above belief is the experience of Schauffler[36] who reports two small series, one of 84 untreated patients in whom 34.5 per cent had resultant retroversion and the other 72 treated patients, with 47.2 per cent of resultant retroversion. The treated patients followed a routine of ventral position in bed, knee-chest on eighth day twenty minutes twice a day, the camel walk on the eighteenth day, and abdominal exercises in the upright position. It has been estimated by various observers that the incidence of retroversion is between 18 and 40-odd per cent. Peckham[37] reports 18.25 per cent retroflexed at six weeks' postpartum and 16.82 per cent at one year. Eichner[31] reports 25.1 per cent at the first examination, three weeks' post partum, the percentage increasing with parity from 20 to 41.2 per cent. In quoting Stacey, Abbott[33] states that there are 20 per cent of retroversions in nonparous, and from 30 to 35 per cent in parous women. He also states that 50 per cent of the patients have no symptoms. Backache, per se, in the presence of retroversions, has been generally over-emphasized and believed to be directly associated with the displacement. This belief has led to too many unwarranted surgical procedures by the general surgeon. We feel it bears repeating that too little emphasis is placed on the use of the Smith Hodge pessary, not only as a curative, but more especially as a diagnostic procedure. Abbott[33] reports 50 patients operated upon for backache, with 16 still having pain after the suspension, and states that this indicates the necessity of an orthopedic study, and further recommends the pessary as a test to see what may be expected after an operation. Peterson[38] also emphasizes the value of the orthopedic relation

to backache even in the face of retroversion and reports a decrease in operative incidence on retroversion due to this fact. Fullerton[39] states that backache is more often due to a strained pelvic girdle than to a retroversion, and recommends a strong abdominal girdle, giving support at the level of the greater trochanters. In a paper by Sturmdorf,[40] Ward is quoted as saying that backache in 15 per cent of gynecologic patients is of orthopedic or of nonsurgical nature. In the same paper Theilhaber of Munich, and Cabot of Boston emphasize the existence of symptomless uncomplicated retroversion of the uterus. Bullitt[40] estimates that 15 per cent of the surgically corrected retroversions continue to suffer from backache. Hurd[40] in 1,000 patients with retroversion found only 17 per cent who complained of backache and concluded that this fails to verify backache as a classical symptom of retroversion. Sturmdorf in further quoting Hurd reports that out of 100 patients operated upon there were 40 per cent immediate failures and 12 per cent symptomatic failures.

A fair-sized group of our patients were found to have symptoms directly referable to pelvic joints attendant upon pregnancy. These patients were treated orthopedically. Discussion of treatment of patients with symptomatic relaxation of the pelvic joints is, of course, beyond the realm of this paper. However, we would like to emphasize the importance of this condition and the possibility of confusing the symptoms of separation of the symphysis and of third-degree retroversion.[41]

It has not been until recent years that much attention has been placed on the care of the bladder during and after labor. It was not uncommon ten years ago to find a considerable number of post-partum atonic bladders, necessitating much in the way of treatment. Though we know that a full bladder militates frequently against normal progress of labor, we find it essential not only from this point of view, but also from the possible resultant atonic bladder, to catheterize, periodically, the patient during labor, especially when analgesic drugs have abolished the normal stimulus to void. Needless to say, all patients are catheterized just before delivery. Following delivery the patient is catheterized at eight hours if unable to void. Subsequent to this, if at the next eight-hour period the patient voids only a small amount, she is catheterized for residual, and if she has a residual of over 2 to 5 ounces, her bladder residual is checked carefully after each voiding until the residual is under two ounces. If, however, at the end of seventy-two hours, there is still a residual of over 5 ounces an inlying catheter is inserted, being kept in position for five days after which it is removed and the patient is checked eight hours later for residual. It is comparatively rare to note a residual after this treatment. In fact, the use of the inlying catheter has been very infrequent during the past half dozen years. This routine as described above has greatly reduced the incidence of atonic bladders with resultant infection. In Table XIII one notes that 95.25 per cent of our patients at six weeks had no bladder symptoms or dysfunction.

TABLE XIII. URINARY SYMPTOMS

	NORMAL	DYSURIA	FREQUENCY	FREQUENCY AND DYSURIA	INCONTINENCE	URGENCY
Cases	1905	58	12	3	18	6
Per cent	95.25	2.9	0.6	0.3	0.9	0.3

It is interesting to note that of the 2,000 patients studied only 6.25 per cent were referred to the hospital for some type of operation. The reasons for transferring to the hospital are shown in Table XIV.

TABLE XIV. PATIENTS REFERRED FOR OPERATION

	REPAIR OF CERVIX	VAGINAL PLASTIC	FIBROIDS	OVARIAN CYSTS	SUSPENSION	STERILIZATION	OTHER PATHOLOGY	NONE
Cases	45	13	3	1	3	3	58	1875
Per cent	2.25	0.65	0.15	0.05	0.15	0.15	4.9	93.75

CONCLUSIONS

1. Two thousand consecutive admissions to the Boston Lying-in Hospital have been studied.
2. Emphasis is placed on conservatism in obstetrics as being most instrumental in the future well being of the patient.
3. A morbidity of 5.5 per cent is reported.
4. Analgesics in labor are recommended.
5. Manual dilatation of the cervix is discouraged.
6. The incidence of operative obstetrics has been kept very low.
7. Episiotomy, preferably median, is encouraged as a routine procedure.
8. Immediate repair of the cervix except in cases of hemorrhage is considered as unnecessary and creating an unnecessarily high morbidity.
9. Use of vaginal douches, silver nitrate, and electrocautery is encouraged.
10. Third-degree retroversions should be treated only when symptomatic and then by the use of the Smith Hodge pessary before resorting to surgery.
11. The bladder should be watched carefully during labor and immediately afterwards and treated to prevent atonicity.

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SICKLE-CELL ANEMIA IN PREGNANCY*

A Review of the Literature and Report of Six Cases

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SICKLE-cell anemia is an hereditary blood dyscrasia peculiar to the negro race, although there have been reports of isolated cases in white families (Greenwald and Burrett[1]). The first complete description of this disease was given by Herrick[2] in 1910. Although the blood of 8 per cent of the negroes has a sickle-cell trait, only 0.8 to 1 per cent develop true sickle-cell anemia. The occurrence of this type of anemia in pregnancy has been reported only on a few occasions.

Sydenstricker[3] found sickled red cells in the cord blood of two infants whose mothers had this disease. Yater and Mollari,[4] Lash,[5] Richter,[6] Sharp and Schleicher,[7] Killingsworth and Wallace,[8] Lewis,[9] Sodeman and Burch,[10] and Page and Silton[11] all contributed case reports of this anemia during pregnancy. Our 6 cases, included herewith, make a total of 17 reported pregnancies with this anemia. A study of these 17 cases with a consideration of their previous pregnancies makes it possible for the first time to offer a detailed analysis of how this anemia affects pregnancy.

CASE REPORTS

Case 1.—E. W., a 22-year-old, colored, gravida i, was admitted to the Obstetric Service of the Cook County Hospital on Jan. 17, 1939. She complained of chilly sensations for six days, followed by a mild cough with white mucoid expectoration and chest pain in the lower right anterior surface. Last menstrual period occurred April 4, 1938, and she was now full term. Past history was essentially negative except for attacks of joint pains during childhood that resembled rheumatic fever.

The patient appeared acutely ill and markedly dyspneic. Her temperature was 101.6° F., pulse 108, respirations 60, and blood pressure 128/84. The lungs showed a faint friction rub in the right base anteriorly with impaired resonance and diminished breath sounds over the right lower lobe posteriorly. The fundus was three fingers below xiphoid, position L.O.A., and fetal heart tones were 160. A tentative diagnosis of right lower lobe pneumonia was made. Roentgenogram of the chest showed only moderate increase of the markings bilaterally with no significant areas

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of consolidation. The only recorded blood examination was a white count of 22,500. A moderate to marked pallor of the conjunctivae was noted, and later the sclerae had an icteric tinge. There was an old scar over the left tibia, 3 by 5 cm. The sputum contained relatively few pneumococci and could not be typed with any known sera. The urine, Wassermann, and blood cultures were negative.

The temperature remained around 102° F., and the respiration varied between 40 and 20 per minute. Since typing with known pneumococcic sera failed, the patient was given sulfapyridine therapy on the next day. On Jan. 19, 1939, at 10:30 A.M. the membranes ruptured spontaneously and the patient went into labor. The fetal heart tones disappeared about an hour after onset of labor. After sixteen hours she delivered a somewhat macerated stillbirth spontaneously. The post-partum blood pressure was 140/92. Her immediate condition was only fair; she failed rapidly and died six hours later, fifty-six hours after admission.

Fig. 1.—Sickle-shaped red cells seen in the intramuscular spaces of the myometrium. The latter shows hypertrophy changes of pregnancy.

Post-Mortem Examination.—(Prosector: J. D. Kirschbaum.) The important features of the anatomic diagnosis were as follows: sickle-cell anemia, marked hepatosplenomegaly, post-partum beginning involution of the uterus, parenchymatous degeneration of the myocardium, atelectasis of the lungs, slight passive congestion of the left lower pulmonary lobe, marked passive congestion of the liver, spleen, and kidneys, and hyperplastic bone marrow.

The microscopic sections of the spleen revealed very compact lymphatic tissue without signs of proliferation and forming small concentric, sharply demarcated coats around the trabeculae and arterioles. Most of the sinusoids of both the liver and spleen were stuffed with conglomerated red blood cells of sickle shape. There was very little phagocytosis of the red blood cells. The bone marrow showed very active myelopoiesis and erythropoiesis with numerous megakaryocytes. All the tissues in the body showed sickling of many erythrocytes. Sickle-shaped red cells were seen within the muscle spaces of the post-partum uterus (Fig. 1).

CASE 2.—M. W., a 30-year-old, colored, gravida i, had her last menstrual period Dec. 23, 1938, and was due on Sept. 30, 1939. Her prenatal course had been practically normal. She had attacks of so-called "rheumatic fever" ever since the

age of four, with frequent recurrences of joint pains. Her sclerae were frequently icteric. This was more pronounced whenever she had a "cold." None of her five brothers and sisters lived to be over thirty-one years of age. On Aug. 31, 1939, she was admitted to the hospital with the complaints of chills for four days, followed by a dry hacking cough, pain in the chest, and shortness of breath.

She was acutely ill with temperature of 102.6° F., pulse 136, respirations 36, and blood pressure 124/106. The sclerae were icteric and the conjunctivae pale; her teeth were in poor condition and pharynx was slightly reddened. The respirations were shallow and limited on the left side, with increased tactile and vocal fremitus, tubular breathing, dullness, pectoriloquy over the left lower lobe. The spleen was palpable. The uterus was three fingers below the xiphoid; fetal position was L.O.T. and fetal heart tones were 150 per minute.

The laboratory findings on admission were as follows: The urine contained albumin three-plus, urobilinogen four-plus, and scattered white blood cells and hyaline and granular casts. The blood serum was highly colored and the icteric index showed thirty units. Hemoglobin was 50 per cent (Sahli), red cell count 2,100,000, and white cell count 37,000. Differential white count showed 87 per cent polymorphonuclears, 8 per cent lymphocytes, and 5 per cent monocytes. There was also 8 per cent sickling and 23 per cent immature red blood cell forms in the dry smear. A chest x-ray taken that day revealed some cardiac enlargement and findings somewhat suggestive of bronchopneumonia. A marked osteoporosis in the bones of each shoulder joint was noted.

The clinical diagnosis of sickle-cell anemia in the acute phase, left lower lobar pneumonia, and moderate toxemia of pregnancy was made. The patient improved gradually with sulfapyridine therapy supplemented by oxygen and repeated blood transfusions. Typing for pneumococci was unsuccessful. Two days after admission the fetal heart tones could no longer be heard. The following day the patient went into labor and six hours later spontaneously delivered a macerated stillbirth that weighed slightly over five pounds. The post-partum blood pressure was 110/74. The improvement continued after repeated transfusions which totaled 4,000 c.c. of preserved citrated blood.

About three weeks post partum, the blood study revealed: hemoglobin 68 per cent, red cell count 3,660,000, white cell count 10,500, and reticulocytes 4.8 per cent. Differential smear revealed 62 per cent polymorphonuclears, 4 per cent eosinophiles, 27 per cent lymphocytes, and 7 per cent monocytes. Anisocytosis, and poikilocytosis four-plus and polychromatophilia were also seen. The sickling was four-plus in the wet stain and 70 per cent in the hanging drop. Her weight remained constant at 98 pounds. When the patient was seen in the clinic two months later, her hemoglobin was 60 per cent, red blood count, 2,870,000 with persistent marked sickling in the moist preparation and the white blood count was 11,400.

CASE 3.—E. S., an 18-year-old, colored, gravida i, due on Feb. 6, 1940, first entered the obstetric service on Nov. 16, 1939. She complained of shortness of breath, pain in the left chest, and blood-streaked sputum. Her eyes were frequently "yellow." Recently she had two attacks of left lobar pneumonia, the last one occurring in the second month of this pregnancy, when the sickle-cell anemia was discovered. Upon admission she was acutely ill with a temperature of 100° F. (rectally), pulse 100, respiration 55, and blood pressure 124/82. She appeared frail; her weight was never over 100 pounds, even in late pregnancy. The sclerae were icteric and the pharynx was slightly injected. A soft systolic murmur was present over the apex of the heart and the second pulmonic tones were accentuated. There was a slight enlargement of the heart to the left. Both bases of the lungs had impaired resonance and moist crepitant râles. The uterus was the size of a six and one-half months' pregnancy.

The laboratory study showed that the urine was normal and the blood Kahn was negative. The chest plate showed an enlarged heart with infiltrative changes in both lower lung fields, especially marked on the left side. The blood studies revealed hemoglobin 44 per cent, red blood count 2,860,000 and white blood cells 17,500. Moist coverslip preparations showed 50 per cent sickling. The differential count

revealed: polymorphonuclears 61 per cent, metamyelocytes 1 per cent, basophiles 1 per cent, lymphocytes 28 per cent, and monocytes 9 per cent. Eight per cent of the red blood cells were nucleated. Anisocytosis was three-plus, macrocytosis two-plus, and polychromatophilia one-plus. The reticulocyte count was 26.8. A diagnosis of left lower lobar pneumonia in a patient six and one-half to seven months pregnant with sickle-cell anemia was made. She was treated with sulfapyridine, fluids, and two blood transfusions, and she made a quick uneventful recovery within two weeks. She was discharged back to the prenatal clinic where her prenatal course was observed.

On Jan. 3, 1940, she was readmitted to the hospital because of a sudden rise in blood pressure to 170/128, dizzy spells for three or four days, and pedal edema for the past week. The urine showed three-plus albumin and a few red blood cells. The hemoglobin was now 50 per cent, red blood count 2,460,000, white blood count 14,750, with 66 per cent sickling and 21 per cent nucleated red blood cells. The differential count was normal. Blood chemistry showed the nonprotein nitrogen to be 28 mg. per cent, and the uric acid slightly elevated to 6.8 mg. per cent.

She was placed on conservative toxemia management. Fundoscopic examination showed changes in the eyes that were interpreted to be due to arteriosclerosis with a possible syphilitic background. Her blood pressure gradually improved; after nine days it was 120/78 and she was discharged back to the prenatal clinic. The diagnosis at that time was a pre-eclamptic toxemia.

Five days later she was admitted to the hospital for the third time with ruptured bag of waters and in active labor. Her blood pressure was now 186/122. She was treated with intravenous hypertonic dextrose and magnesium sulfate and morphine. She delivered spontaneously a three-pound twelve-ounce female infant after a labor of five hours and ten minutes. The baby was in good condition, and blood counts made on the infant at various intervals were normal. The patient's post-partum course was complicated only by the development of a low grade endometritis which gradually subsided. Her blood pressure dropped to 142/90 on the fourth day. She received two blood transfusions, 500 c.c. each, during puerperium and was discharged on the eleventh day.

The blood count on the day of discharge revealed 45 per cent hemoglobin, 2,090,000 red cells, and 13,600 white cells. The stained smear showed 75 per cent polymorphonuclears, 1 per cent basophiles, 17 per cent lymphocytes, 6 per cent monocytes, 1 metamyelocyte, 3 nucleated reds, presence of target cells, hypochromia one-plus, polychromatophilia two-plus, anisocytosis with macrocytosis and poikilocytosis two-plus. The urine showed no albumin on discharge.

CASE 4.—A. O., an 18-year-old, colored, gravida i, menstruated last on Feb. 1, 1940. One week before admission to the hospital, she felt feverish, developed marked urinary frequency, and had a backache on the right side. She was admitted to the hospital on June 27, 1940, with a temperature of 102.6° F., and pulse 120. Her chief complaint at this time was backache. The uterus was about the size of a six months' gestation. The patient appeared frail and delicate; otherwise the physical findings were negative.

The admission diagnosis of pyelitis was confirmed by a catheterized urine specimen that showed many clumped pus cells. Urinary culture revealed *B. coli.* The initial blood examination showed a red count of 2,900,000, hemoglobin 51 per cent (Sahli), and a white count of 20,100. One week later the red count was 2,220,000, hemoglobin 42 per cent (photoelectric colorimeter), and the white count 47,000. The differential count enumerated 91 per cent polyneutrophiles, of which 39 had band forms, 3 per cent metamyelocytes, and 6 per cent lymphocytes. In addition, anisocytosis, polychromatophilia, marked basophilic granulations of the granulocytes or a toxicity of four-plus, and marked sickling was observed.

During her stay in the hospital, the essential therapy was directed to overcome the infection and the anemia. Sulfanilamide was given for the infection. For the anemia, she was given six transfusions of 500 c.c. each of citrated blood, liver extract, iron ammonium citrate, nicotinic acid, dilute hydrochloric acid, and high caloric diet when the patient was able to retain foods.

The clinical course was as follows: Two days after admission the temperature dropped to normal, but after five afebrile days the temperature rose to 102.2° F. and spiked irregularly between normal and 104.2° F. The patient coughed considerably at times, but examinations of the chest and x-ray findings were negative. After six days of hyperpyrexia, the temperature gradually but irregularly declined to normal. At this time (the eighteenth hospital day), fetal heart tones disappeared. Two days later she spontaneously delivered a macerated fetus of four and one-half months' size. After the third puerperal day the temperature gradually rose to 102.6° F. and after four days subsided slowly to normal.

On the twenty-sixth hospital day the hemoglobin declined to 24 per cent, and the red count was 1,670,000 and the white count 97,000. At this time she was probably passing through a hematologic crisis. Thereafter the blood picture gradually improved and shortly before her discharge, the hemoglobin was 60 per cent. She was discharged on the twenty-seventh post-abortal day.

CASE 5.—S. P., 20 years of age, colored, gravida i, was first seen in the prenatal clinic on March 25, 1940. Her last menstrual period occurred on Dec. 21, 1939, and she was due to deliver Sept. 28, 1940. She had frequent attacks of rheumatic fever, and joint swelling since five years of age and had been refused life insurance because of an alleged "heart-leak." No abnormal physical findings were noted at first prenatal visit. The Kahn test was negative. The ante-partum clinical course was essentially normal.

She was admitted to the hospital on Sept. 13, 1940, having what proved to be false labor pains. The temperature was 100.6° F. with a pulse of 96. For the first time a diagnosis of rheumatic heart disease with a double mitral lesion and aortic regurgitation was made. Two days after admission the patient went into true labor and after a very short labor delivered a normal female child weighing 7 pounds. This baby had a normal blood picture and no sickling. In the early puerperium the mother had an icteric tinge to her sclerae and the liver was palpable two fingers below the costal margin. Despite a low degree of septic morbidity she made a normal recovery.

The essential laboratory findings were as follows: Two days after delivery the blood picture showed 2,180,000 red cells, 64,000 white cells, and 34 per cent hemoglobin (Sahli). The wet preparation of the blood smear revealed 60 per cent sickling in the red cells. The differential white count was 85 per cent polyneutrophiles, 2 per cent metamyelocytes, 1 per cent myelocytes, 3 per cent monocytes, 9 per cent lymphoctyes, and one immature cell. It was also observed that the red cells showed anisocytosis, toxicity one-plus, and 87 normoblasts, of which two were stippled. One week later there was marked improvement in the red count and the white count was 18,000; the sickling was markedly decreased.

The treatment administered during the patient's stay consisted of 2 transfusions of 500 c.c. of blood, thiamine chloride 1 c.c. twice daily, liver extract and antianemic diet.

CASE 6.—E. N., 26 years of age, colored, para vi, gravida vii, entered the hospital on Nov. 29, 1940, in labor at term. She had been a patient in the Medical Division of the Cook County Hospital in November, 1939, when she had recovered from pneumonia. At that time sickle-cell anemia had been noted. Her blood count then was 2,400,000 red cells, 36 per cent hemoglobin (photoelectric), and 43,900 white cells. Four nucleated reds and other abnormal forms were noted. She was later followed by the anemia clinic and given iron therapy with good clinical effects. Despite this, low grade anemia prevailed, ranging from 2,860,000 to 4,600,000 red cells. Aside from the anemic picture her prenatal course was uneventful. Previous to this pregnancy, however, she had had frequent rheumatic pains and had been receiving therapy from private physicians for an alleged, but unclassified, anemic condition.

Physical examination revealed no abnormal findings. Two small scars were present on the anterior surface of the left leg. Her labor terminated uneventfully in five

hours with delivery of a normal male full-term infant. The puerperal course was uneventful except for the development of a low grade fever up to 101° F. after the sixth post-partum day, with no accountable cause. At the present time she is twenty-two days post partum.

Laboratory findings on the day of admission revealed 3,220,000 red cells and 50 per cent hemoglobin (photoelectric). On the eleventh post-partum day, the red count was 2,730,000, hemoglobin 49 per cent, and white count 29,900. At this time the wet smear again showed sickle cells. There were many abnormalities of color, shape, and size of the red cells and many nucleated forms. She was treated with antianemic diet, iron, and blood transfusions (1,500 c.c.). On the eighteenth day, the red count was 3,910,000 with 50 per cent hemoglobin and 6,900 white cells. Her condition was much improved. At the present time she has sufficiently recovered to be discharged from the hospital. Blood studies on the infant have failed to reveal any sickling tendency up to the present time.

DISCUSSION

Although the etiology of sickle-cell anemia is unknown, it is believed to be a familial disease transmitted by both sexes as a dominant Mendelian characteristic. Gumbiner[12] states that these cases are seen only in the younger age groups, since the majority of persons with active signs of the disease die before they reach thirty years of age, either from the effects of the anemia or from intercurrent infections. This is verified in Table I, summarizing the clinical features of all reported cases of sickle-cell anemia during pregnancy. Here it can be seen that the age of the youngest patient was 18 and that of the oldest was 30, the average age being 22.4. By virtue of the shortened life expectancy of these patients, only 3 of 15 have become multiparas. The viable stage of gestation was reached by 13 of the entire group of 17 mothers. The various theories as to the pathogenesis of this disease, proposed by Jaffe[13] and by Anderson and Ware,[14] have been discussed by Lash. The essential pathology is found in the spleen, bone marrow, liver, kidneys, and cardiovascular system. Early in the disease the spleen is large and swollen, and later it becomes smaller with marked siderofibrosis. The bone marrow is typically hyperplastic. In all the organs studied a large proportion of the red cells showed sickling. Various authors describe the so-called "abdominal crises" due to the resultant infarction in various abdominal viscera (Yater and Mollari, Campbell[15]). Another important terminal pathologic feature is the complicating tendency to infection, especially pneumonia, due to the lowered resistance of the patient because of the severe anemia.

In the 17 reported sickle-cell anemias with pregnancy, there were 5 deaths, 4 of which were subjected to post-mortem examination. "Abdominal crisis" was the terminal cause of death of one patient (Yater and Mollari) and was postulated in another (Lash), although in the latter case an unaccountable postoperative shock prevailed. In the third death the predominant pathology consisted of multiple thrombi, and a complicating pulmonary embolus with multiple infarcts terminally (Page and Silton). Puerperal sepsis claimed the fourth patient six weeks post partum.* The predominant fatal pathology found at autopsy in one of our series (Case 1) was marked hepatosplenomegaly and parenchymatous degeneration of various organs including the heart.

*Disclosed on personal communication with the author, W. P. Killingsworth.

Clinically, certain symptoms and findings are frequently seen. The patients are usually thin and underdeveloped. Four of our patients in this report weighed 100 pounds or less, even when pregnant. The complaints usually consist of frequent attacks of respiratory infections (usually pneumonia), joint and muscle pains (reported 9 out of 14 times), vague abdominal pains with nausea and vomiting, occasional fever, ulcers of the legs, jaundice (usually noticed for many years) and other cardiorespiratory symptoms associated with a severe anemia. The disease is characterized by remissions and exacerbations. During the acute phase of "abdominal crisis" the disease must be differentiated from the acute abdomen (Campbell), rheumatic fever, tuberculosis, syphilis, and obscure anemias (Killingsworth and Wallace).

During pregnancy these patients frequently developed hypertensive or pre-eclamptic toxemia. Of the 13 patients in whom blood pressure recordings were reported, 4 (Lash, Sodeman and Burch, Cases 2 and 3) showed a mild to marked tendency in that direction. The puerperal septic morbidity is frequent observed, and all of our patients had a febrile course.

Roentgenologically, osteoporosis is commonly seen in the long bones with the marrow cavity replaced by radially placed bone formations simulating individual hairs standing on end, while the skull shows increased thickness of the calvarium, loss of continuity of the outer table and replacement of the marrow cavity by altered bone formations (Harden[16]).

The diagnosis, of course, rests finally on the blood picture. During the acute episodes of the disease there is a profound anemia, the red count usually being below 2,500,000 with a corresponding decrease in hemoglobin. A moderate to very marked leucocytosis is seen far in excess of what one would ordinarily expect during pregnancy. The red cells are normocytic and normochromic with a tendency toward macrocytosis. There is an increase in reticulocytes, and presence of nucleated red cells with other evidence of marked regeneration. Most of the erythrocytes are sickle shaped, which is best demonstrated on moist coverslip preparations after standing twelve to eighteen hours. Then, practically 100 per cent will assume the abnormal shape characteristic of the disease. With an increase in oxygen tension, there is a tendency of the cells to assume a normal shape, whereas when the oxygen tension is lowered, the cells again become sickled (Hahn and Gillespie[17]).

Prognostically, the disease casts a gloomy picture. The majority of patients die before the age of thirty. Pregnancy apparently has an unfavorable effect upon a mother having sickle-cell anemia. In 15 cases where the clinical course of the mother was recorded, 5 did not survive the pregnancy, a mortality ratio of one to three. It has recently come to our attention that at least 2 additional mothers have died sometime subsequent to the publication of their case reports by other authors in the literature (Sharp and Schleicher, and Page and Silton).

The prognosis for the fetus in utero is also unfavorable. From the available data in 15 mothers, 5 (33 per cent) had one or more abortions. These mothers had 37 pregnancies of which only 25 were carried to

TABLE I. TABLE OF REPORTED CASES IN LITERATURE OF SICKLE-CELL ANEMIA AND PREGNANCY

AUTHORS	AGE	PARA	GRAV.	ESSENTIAL COMPLAINTS	HB %	R.B.C.	SICKLING	BABY	MOTHER	TREATMENT
Sydenstricker (1924)	Not stated							Sickling in cord blood	Course unknown	Not stated
	Not stated							Sickling in cord blood	Course unknown	Not stated
Yater and Mollari (1931)	25	0	ii	Pains in legs	44	2.57	Active sickling	Six months spontaneous abortion	Died in "abdominal crisis" (autopsy)	Liver and iron
Lash (1934)	21	0	i	Feet swollen; B.P. 145/105	75	3.45	In autopsy sections	Term live baby with sickled red cells	Prolonged labor; died 6 hours postoperatively (autopsy)	Cesarean section
Richter et al. (1934)	21	0	i	Chills and fever on second post-partum day	67	2.17	Sickling noted	Term live baby	Spontaneous delivery; improved later	Oral equine liver
Sharp and Schleicher (1936)	26	0	i	Not stated	25 65	0.90 3.60	Extreme sickling	Term live baby; sickling after 4 months	Normal recovery; improved*	Blood transfusions
Killingsworth and Wallace (1936)		vi	xi	Previous stillbirths; symptoms not stated; four previous abortions	Not stated			Stillbirth; sickle cells in bone marrow	Died six weeks post partum; puerperal sepsis†	Not stated
Lewis (1937)	25	0	iv	Rheumatic heart disease and associated symptoms	40 53	1.60 2.50	50% sickling	Hysterotomy at 4 months	Improved	Diet, iron, liver, hysterotomy

Sodeman and Burch (1938)	23	ii	iii	Axillary pain, dyspnea, vertigo; B.P. 140/80	40 45	2.10 2.67	Marked sickling	Term live baby; all babies had sickled red cells	Normal recovery; improved later	Iron, intramuscular liver
Page and Silton (1939)	19	0	i	Jaundice, weakness, joint and epigastric pain	42 54	1.86 2.35	Marked sickling	Term live baby	Normal recovery; improved later‡	Transfusions (7) iron-copper (lextron)
	20	0	i	Acutely ill; jaundice; pneumonia	35	1.92	In autopsy sections	Twin 5 mo. pregnancy	Died undelivered (autopsy)	Died 22 hours after admission
Kobak, Stein, and Daro (1940)	22	0	i	Rheumatoid pains; jaundice; acute pneumonia			In autopsy sections	Term macerated stillbirth	Died 6 hours post partum (autopsy)	Sulfapyridine
	30	0	i	Rheumatoid pains; lobar pneumonia; pre-eclampsia; B.P. 160/92	50 68	2.10 3.66	70% sickling	8½ month stillbirth	Recovered from pneumonia post partum	Sulfapyridine, oxygen, blood (4,000 c.c.)
	18	0	i	Lobar pneumonia; pre-eclampsia; B.P. 186/122	44 50	2.86 2.46	50% sickling 66% sickling	7½ month premature live baby; no sickling in R.B.C.	Normal recovery; improved later	Sulfanilamide blood, treatment of toxemia
	18	0	i	Pyelitis	24 50	1.67 2.90	Marked sickling	5½ month abortion; macerated fetus	Improved postabortal	Sulfapyridine, blood, vitamins, diet
	20	0	i	Rheumatic fever and pains; rheumatic heart disease	34	2.18	60% sickling	Term live baby, no sickling	Improved post partum	Blood, vitamins, diet, iron
	26	vi	vii	Previous stillbirth; rheumatic pains; weakness	36 70	2.40 4.60	Moderate sickling	Term live baby, no sickling	Improved post partum	Blood, vitamins, diet, iron

***Died three years later following hysterectomy.**
†Additional information by personal communication.
‡Died of pneumonia one and one-half years after publication.

viability. Nineteen of these viable babies were born alive, whereas 6 were macerated stillbirths. Among all live births reported in the literature, the blood of at least 8 of the babies developed sickled red cells. Follow-up studies may have revealed a greater number. Lewis comments that the pregnancy caused an exacerbation of the sickle-cell anemia and that the anemia may cause abortions. Sodeman and Burch believe that sickle-cell anemia decreases fertility in the female. Their contention is partially corroborated by the literature which shows that of 15 women of known parity, 10 were pregnant for the first time. Of the remaining 5 women, only 3 had more than 1 live child. The cause of this lack of fertility is not completely understood. The anemia itself may be a cause of lowered fertility and abortion. The presence of anemia for long periods of time, even through the adolescent period into adult life, may have a profound effect upon the reproductive functions. Aside from the mere presence of this anemia, the disease may affect the reproductive function in some other unknown manner (Sodeman[18]).

Therapeutically these patients have been subjected to various drugs and surgical procedures. It is significant that all patients who survived pregnancy and labor received intensive antianemic therapy. Seven of these patients received multiple blood transfusions. With the easily available supply of blood transfusions through the blood bank at the Cook County Hospital, this form of therapy has been tested with a measure of success. We believe their improvement is only temporary, however. This improvement is due (according to Josephs[19]) to a certain factor present in normal plasma which temporarily maintains normal blood formation and destruction. General supportive measures, such as rest and a diet high in calorie and vitamin content, aid in bringing about improvement. The treatment of any complicating condition, such as intercurrent infections with sulfanilamide or a toxemia of pregnancy, is given as indicated.

SUMMARY AND CONCLUSIONS

1. Six additional cases are added to the existing medical literature on sickle-cell anemia during pregnancy, making a total of 17 cases. Almost one-half of these cases are reported from the Cook County Hospital, which admits annually about 27,000 negroes to its various services and about 3,500 negroes to its obstetric services.

2. An analysis of the reported cases of pregnancy, complicating this type of anemia, has been made, and the pertinent features have been discussed.

3. Sickle-cell anemia during pregnancy is a disease which, while rarely reported at present, is becoming more generally recognized.

4. Most of these cases present themselves in their first pregnancy and only 3 have had more than one child. The exact mechanism of this apparent lack of fertility is not completely understood.

5. Of the 13 cases in which the blood pressure recordings were reported, 4 showed a mild to marked hypertensive toxemia of pregnancy.

6. Patients with this disease have a short life expectancy, being subject to intercurrent infections, especially respiratory, and to the de-

generative effects of the severe anemia on the cardiovascular system. At least one-third of the mothers died during or shortly after the pregnancy.

7. This disease has an injurious effect on pregnancy, since one-third of the women had one or more abortions and about one-sixth of the pregnancies terminated in the delivery of macerated stillbirths.

8. At least one-third of the babies were known to have sickling phenomenon.

9. The puerperium is characterized by a tendency toward septic morbidity; all of our patients had a febrile course.

10. The treatment is not specific, various forms of therapy being temporarily effective. Intensive antianemic therapy and repeated transfusions are beneficial.

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DISCUSSION

DR. RICHARD H. YOUNG.—The anemia of this disease is usually very severe. It is a normocytic normochromic anemia, i.e., there is no change in the size of the red cells or in the hemoglobin content. These points should help to distinguish it from some of the other anemias in pregnancy. Reticulocytes are present during the active phase of sickle-cell anemia. The reticulocyte percentage can, therefore, be used as an index of hemolytic activity. The disease is characterized by remissions and relapses and the patients give a history of periods of ill health and good health throughout their lives.

The sedimentation rate in individuals with sickle-cell anemia is usually normal in character. If there is a high sedimentation rate, there is usually some complication.

In the authors' series there were 5 cases of pulmonary disease. I feel that some of the cases that were diagnosed as pneumonia were probably pulmonary infarctions. In the full paper, I read the complete clinical histories of those patients that died, and I felt the cause of death was probably a pulmonary infarct.

Blood transfusions are the best available type of treatment. The use of iron and liver is not on a sound basis. There is no loss of iron to the outside, and, therefore, no deficiency of iron. There is no macrocytic anemia, so you would not expect liver to be effective.

DR. WALTER SCHILLER.—An analysis of these cases may throw some light on the problem of the way sickle-cell anemia complicates pregnancy.

In the first case the patient died of puerperal sepsis six weeks after delivery. It is probable that the sickle-cell anemia weakened her resistance against the infection. Two other patients, the cases of Yater and Mollari and of Page and Silton, presented a syndrome for which the term "abdominal crisis" was coined. The term "abdominal crisis" refers to the sequelae of multiple thrombosis of mesenteric and pelvic veins.

In cases 4 and 5 autopsies were carried out at the Cook County Hospital. In Dr. Lash's case the patient died of "shock" six hours after cesarean section. In the case reported by Drs. Kobak, Stein, and Daro, the patient delivered a macerated baby at term and died six hours later. In both of these cases gross and microscopic findings were strikingly similar. The spleen and liver were enlarged from passive congestion, and the vessels all over the parenchyma were stuffed with red blood corpuscles. Particularly in the liver, the acinar sinusoids were dilated and partially blocked by clumped and coagulated sickled red blood corpuscles, thus obstructing the passage of the portal blood through the liver. Such obstruction in the liver leads to retention and increase of blood in the intestines and to a reduction of the quantity of blood which reaches the heart and circulation in the periphery.

An upset distribution of the peripheral and intestinal blood was first investigated by Fr. v. Mueller in a condition he called "hepatic shock." Hepatic shock which clinically is due to sudden contraction of the portal vein and its branches can be duplicated in animals by injection of histamine. The abnormality of circulation in the two cases of sickle-cell anemia is analogous to the hepatic shock, but the mechanism is different. In hepatic shock the obstruction is due to active contraction of the branches of the portal vein. In sickle-cell anemia, it is a passive blockade, particularly of the acinar sinusoids by clumped red blood corpuscles. If this blockade develops slowly, it leads to stasis and subsequent thrombosis in the mesenteric veins producing an "abdominal crisis." If it develops rapidly, the clinical picture is the same as in hepatic shock.

From these observations of pregnancy in sickle-cell anemia, it seems that the main danger to the patient does not lie in the anemia or in the exhaustion of the bone marrow but in the blockade of the liver. Shortened clotting time and increased fibrinogen rate, hyperinosis, are well-known physiologic pregnancy changes. If these physiologic changes coincide with the pathologically increased tendency for clumping of sickled red blood corpuscles, blockade of the narrow liver sinuses may occur.

DR. FREDERICK H. FALLS.—In this condition we have an increased coagulability of the blood, and an associated increase in the percentage of hypertension. That is significant in view of the idea that thrombosis or vascular accident in the placenta is the underlying factor in the toxemias of late pregnancy.

I would like to raise the question of whether it is wise to give blood transfusions to patients who have this type of blood dyscrasia? Do we know what is going to happen to the blood that we put into a patient who already has a pathologic condition of the blood-clotting mechanism? I am becoming convinced that the indiscriminate use of transfusions in eclamptogenic toxemia is a bad thing, because of certain fatal cases I have seen after the use of blood transfusion.

I should also like to ask about the fate of the baby and, in particular, the time of death of the baby in cases in which stillbirths occurred. This brings up the question of whether cesarean section might not save the baby. We have a condition here which is fatal as far as the mother is concerned, but the baby has a pretty good chance if delivered. If so and if the baby is viable, why not do a cesarean section and insure the life of the baby even though one would take some additional chance on the life of the mother?

DR. KOBAK (closing).—The combination of sickle-cell anemia with pregnancy, while infrequent, is not as rare as the literature would lead one to believe. Since 1924 when Sydenstricker made his publication, and with the six here presented, there will be a total of 17 pregnancies with sickle-cell anemia reported in the literature. When we communicated with these men concerning the subsequent course of the mother, 2 out of 4 replies volunteered information concerning additional cases

which came to their attention. These men stated that they had now seen 10 additional cases of pregnancy with sickle-cell anemia.

I believe it was our awareness of this anemia that made it possible for us to diagnose our 6 cases during the past two years. Because of this awareness, and the prompt diagnosis, the therapy that was given was helpful in carrying 5 out of 6 of these women past the puerperium. I have a feeling that possibly some of our puzzling deaths that heretofore occurred among negro patients might have been an undiagnosed sickle-cell anemia.

In answer to the question raised by Dr. Falls, we have found that without a doubt transfusions have been very helpful. While one may consider the possibility of some unfavorable action, the sum total was satisfactory.

Examination of the babies' blood showed one out of three with sickle-cell phenomena. In one case this sickle-cell phenomenon did not appear until the fourth month. We do not know how many of these babies may later develop a sickle-cell anemia.

Concerning the use of cesarean section and its value, I cannot answer that question. There is a possibility as suggested by Dr. Schiller that it may throw the patient into shock or crisis. Our policy has been to treat these patients medically and with transfusion therapy; we only used obstetric procedures when the usual indications called for them.

A SIMPLE METHOD OF X-RAY PELVIMETRY

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IT IS not the purpose of this paper to justify the use of x-ray pelvimetry in the scientific practice of obstetrics. This has been ably done by Thoms, Caldwell, Moloy, Steele, and others. Its intention is to describe a method which can be used readily by every physician who handles obstetric cases.

The many excellent methods of x-ray pelvimetry available today are extremely complicated, either from the standpoint of taking the films, or in the interpretation of the finished x-ray plate. They either include complicated tube shifts, grids, stereoscopically taken films, complex mathematical calculations, or some other factor which may confuse the average practitioner, so that he cannot master and readily adopt this procedure.

There are comparatively few today who are able to read a pelvic roentgenogram. This is easily proved by the fact that usually one man on the obstetric staff of even the larger hospitals is assigned to the interpretation of pelvic x-rays. Why should the methods used be so complex that many obstetricians and the great majority of general practitioners cannot interpret the plates accurately?

It was our purpose to find some simple method which could be used generally in private practice. We tried to fulfill the following conditions: (1) No extra expensive equipment should be necessary for either taking or interpreting the pictures; (2) reading of the plate should not require special training; (3) measurements should be between set points, and no differences should exist between different examiners because of ocular variations; (4) the technique of the taking of the x-ray exposures should be simple; and (5) the method should be accurate.

The procedure about to be described is not entirely original, but rather a composite one, in which an attempt is made to incorporate all the better features of the methods already known with some variations which are original.

PROCEDURE

Three plates of the pelvis are taken routinely, a horizontal anteroposterior, a horizontal lateral, and a 45 degree angle exposure of the subpubic arch and side walls. A Potter-Bucky diaphragm and a medium-sized cone are used. No special equipment is necessary except for a metallic ruler which has notches 1 cm. apart. This is placed between the buttocks and partially between the inner surfaces of the thighs for support when taking the lateral exposure.

TABLE I. TECHNIQUE

	KILOVOLT PEAK	MILLI-AMPERES	TIME SEC.	DISTANCE INCHES	TUBE CENTERED	REMARKS
AP	65-75	30	5	30	Midline 8 cm. back of symphysis.	Keep thighs together. Tilt pelvis 45° with pillow doubled in small of back
LAT.	80-90	30	15-40	30	Over hips	Be sure that pelvis is not rotated. Slightly flex thighs. Thighs together
45°	75	30	5	25	Aim at subpubic arch at 45° angle	Flex and abduct thighs so that subpubic angle can be seen. Withdraw pillow

MEASUREMENT AND INTERPRETATION OF THE FILMS

Lateral Plate.—Inasmuch as the metallic ruler lies in the midline, its image on the film will be distorted (enlarged) in the same proportion as all the anteroposterior measurements taken in this plane. To find the true measurement of any anteroposterior diameter, therefore, one needs only to measure the distance between the anterior and posterior landmarks of any plane (inlet, midplane, or outlet), transpose the distance on the image of the ruler on the plate, and then read the true measurement.

To obtain the transverse diameters of the pelvic planes, one should measure the distance between the recognized transverse landmarks of each plane directly on the anteroposterior plate. Inasmuch as the transverse planes of the inlet, midplane, and outlet lie at different distances from the x-ray tube, the degree of distortion of each is different. If, however, the distance from the plate to the transverse plane to be measured is known, the degree of enlargement is easily determined and a true accurate measurement is obtained.

In order to ascertain how far the transverse plane measured is from the table top, the lateral plate is consulted. A baseline is drawn parallel to the film edge that touches the most lateral border of the sacrum. This represents the table top if the patient were lying flat on her back. In order to find how far the plane is from the table top, one need only measure the distance from the plane to the baseline and read the result directly from the ruler image on the plate. If Table II is then consulted, using both the table-top-plane measurement and the transverse measurement of the image on the anteroposterior plate, the true transverse measurement is then determined.

INTERPRETATION OF PLATES

For the sake of clarity, the interpretation of a typical set of plates will be discussed in detail:

1. Measurements.—On the lateral plate, a line is drawn from the upper border of the symphysis to the midpoint on the sacrum where the two white ileopectineal

TABLE II.* MEASUREMENT TO BASELINE. LATERAL PLATE

Transverse measurement of the diameter on the film (anteroposterior plate) CENTIMETERS	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
4.0	3.6	3.5	3.5	3.4	3.4	3.3	3.3	3.2	3.2	3.1	3.1	3.0	3.0	2.9	2.9
4.5	4.1	4.0	4.0	3.8	3.8	3.7	3.7	3.6	3.6	3.5	3.5	3.4	3.4	3.3	3.3
5.0	4.5	4.4	4.3	4.2	4.2	4.1	4.0	3.9	3.9	3.8	3.8	3.7	3.7	3.6	3.6
5.5	5.0	4.9	4.8	4.7	4.6	4.6	4.5	4.4	4.3	4.2	4.2	4.1	4.1	4.0	4.0
6.0	5.4	5.3	5.2	5.1	5.0	4.9	4.9	4.8	4.7	4.6	4.6	4.5	4.4	4.3	4.3
6.5	5.9	5.8	5.7	5.5	5.5	5.3	5.3	5.2	5.1	5.0	5.0	4.9	4.7	4.7	4.6
7.0	6.3	6.2	6.1	5.9	5.8	5.7	5.7	5.6	5.5	5.4	5.3	5.2	5.0	5.0	4.9
7.5	6.8	6.6	6.5	6.4	6.3	6.2	6.1	6.0	5.9	5.8	5.7	5.6	5.5	5.4	5.3
8.0	7.2	7.0	6.9	6.8	6.7	6.6	6.5	6.4	6.3	6.2	6.0	6.0	5.9	5.8	5.7
8.5	7.6	7.5	7.4	7.2	7.1	7.0	6.9	6.8	6.7	6.6	6.5	6.4	6.3	6.2	6.1
9.0	8.0	7.9	7.8	7.6	7.4	7.3	7.3	7.2	7.0	6.9	6.9	6.8	6.6	6.5	6.4
9.5	8.5	8.4	8.3	8.1	7.9	7.8	7.7	7.6	7.5	7.4	7.3	7.2	7.0	6.9	6.8
10.0	8.9	8.8	8.7	8.6	8.4	8.3	8.2	8.0	7.9	7.8	7.6	7.5	7.4	7.2	7.1
10.5	9.4	9.3	9.2	9.0	8.9	8.7	8.6	8.4	8.3	8.2	8.0	7.9	7.8	7.7	7.4
11.0	9.8	9.7	9.6	9.4	9.3	9.1	9.0	8.8	8.7	8.5	8.4	8.2	8.1	7.9	7.8
11.5	10.3	10.1	10.0	9.9	9.7	9.5	9.4	9.2	9.1	8.9	8.8	8.6	8.5	8.3	8.2
12.0	10.7	10.5	10.4	10.3	10.1	9.9	9.8	9.6	9.5	9.3	9.2	9.0	8.8	8.6	8.5
12.5	11.2	11.0	10.9	10.7	10.5	10.3	10.2	10.0	9.9	9.7	9.6	9.4	9.2	9.0	8.9
13.0	11.6	11.4	11.3	11.1	10.9	10.7	10.6	10.4	10.3	10.1	10.0	9.8	9.6	9.4	9.2
13.5	12.1	11.9	11.7	11.5	11.4	11.2	11.0	10.8	10.7	10.5	10.3	10.1	10.0	9.8	9.6
14.0	12.5	12.3	12.1	11.9	11.8	11.6	11.4	11.2	11.0	10.8	10.6	10.4	10.3	10.1	9.9
14.5	13.0	12.8	12.6	12.4	12.2	12.0	11.8	11.6	11.4	11.2	11.0	10.8	10.7	10.5	10.3
15.0	13.4	13.2	13.0	12.8	12.6	12.4	12.2	12.0	11.8	11.6	11.4	11.2	11.0	10.8	10.6
15.5	13.9	13.7	13.5	13.3	13.1	12.8	12.6	12.4	12.2	12.0	11.8	11.6	11.4	11.2	11.0
16.0	14.3	14.1	13.9	13.7	13.5	13.2	13.0	12.8	12.6	12.4	12.2	12.0	11.8	11.6	11.4
16.5	14.8	14.5	14.3	14.1	13.9	13.6	13.4	13.2	13.0	12.8	12.6	12.4	12.2	12.0	11.8
17.0	15.2	14.9	14.7	14.5	14.3	14.0	13.8	13.6	13.4	13.2	13.0	12.8	12.6	12.4	12.2
17.5	15.7	15.4	15.2	14.9	14.7	14.5	14.3	14.0	13.8	13.6	13.4	13.2	13.0	12.8	12.5
18.0	16.1	15.9	15.6	15.3	15.1	14.9	14.7	14.4	14.2	13.9	13.7	13.5	13.3	13.1	12.8

*This table is corrected for the additional 5 cm. from the table top to the plate.
The corrected figures are obtained, using the geometric theorem "in similar triangles, the base is proportional to the altitude."

lines would meet. This is the true obstetric conjugate. The sacral promontory is usually 1 to 2 cm. above this. The distance between these points is measured and transposed upon the ruler on the film. A direct reading is thus obtained.

Next a line is drawn from the midpoint between the ischial spines which joins the line of the obstetric conjugate at right angles. The portion of the obstetric conjugate posterior to the junction is called the posterior sagittal of the inlet. This is measured in the same manner as the obstetric conjugate.

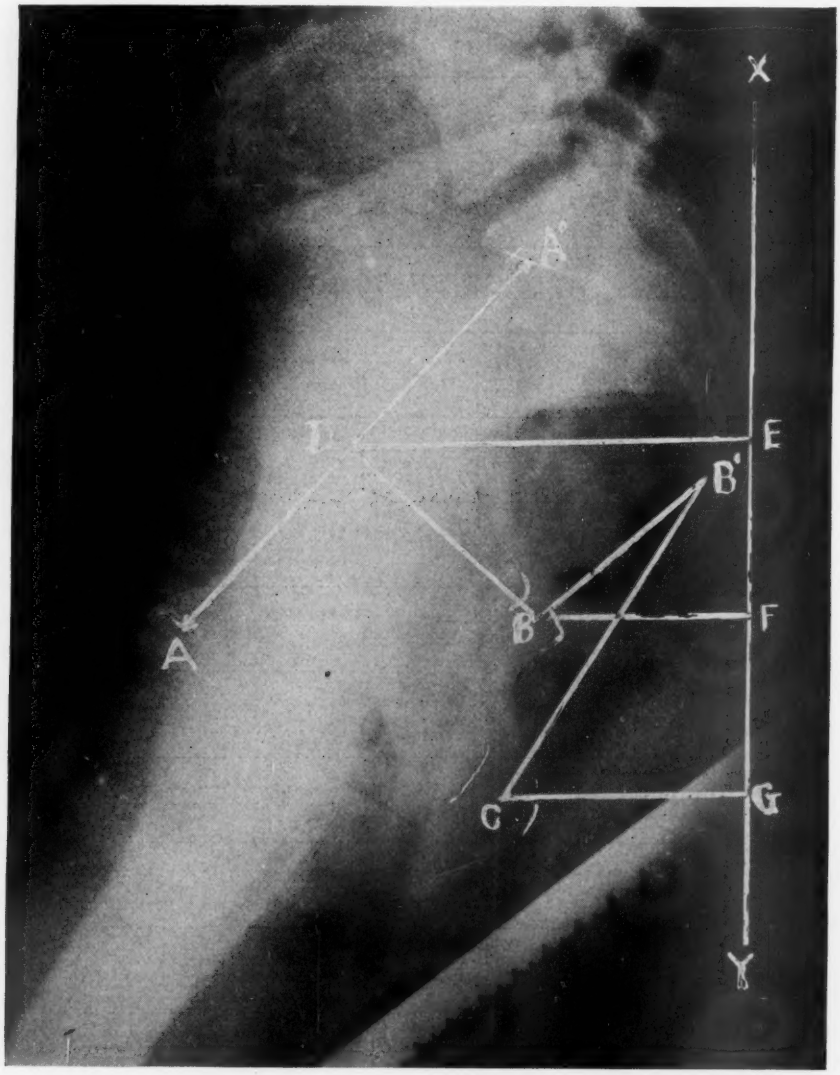

Fig. 1.—Lateral view of the pelvis. *A-A'*, Obstetrical conjugate; *D-A'*, posterior sagittal of the inlet; *B-B'*, posterior sagittal of the midplane; *C-B'*, posterior sagittal of the outlet. *X-Y*, Baseline parallel to film edge; *D-E*, distance from plane of inlet to baseline; *B-F*, distance from midplane to baseline; *C-G*, distance from plane of the outlet to the baseline. Also observe lateral bore, length of the sacrum, sacral curve, pelvic inclination, sacrosciatic notch.

To obtain the posterior sagittal of the midplane, identify the two spines and mark the midpoint between them. The distance is measured between this point and the end of the sacrum, and then read directly from the ruler image on the plate.

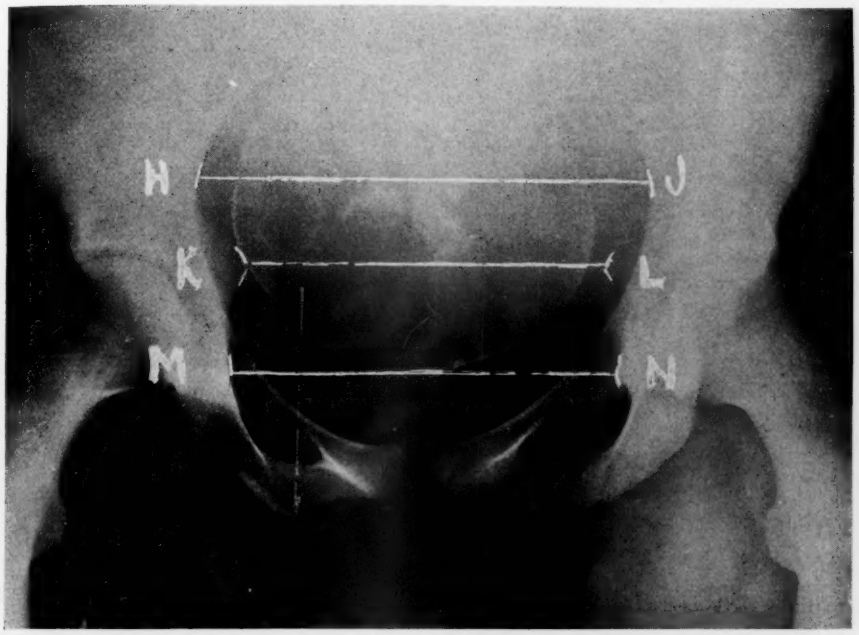

Fig. 2.—Anteroposterior view of the pelvis. *H-J*, Widest transverse diameter of the inlet; *K-L*, interspinous diameter of the midplane; *M-N*, transverse diameter of the outlet. Also observe the shape of both the anterior and posterior portions of the inlet, its symmetry, and the prominence of the spines.

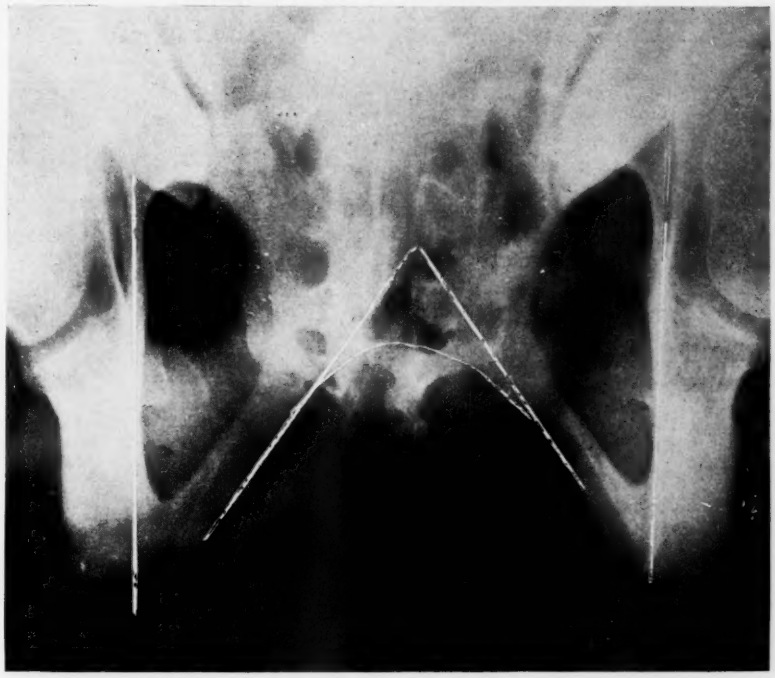

Fig. 3.—Forty-five degree angle view of the pelvis. Observe the direction of the side walls, the shape of the subpubic arch, the width of the subpubic angle, and the depth of the pelvis.

The posterior sagittal of the outlet is measured from the midpoint between the tuberosities to the end of the sacrum, and this again is read directly by transposing the measurement on the ruler on the film. Thus, the diameters of the obstetric conjugate, posterior sagittal of the inlet, midplane, and outlet are obtained.

In order to obtain the transverse measurements, one simply measures with a centimeter ruler on the anteroposterior plate the distance between the widest points of the ileopectineal lines (inlet), the interspinous diameter (midplane), and the intertrochanteric distance (outlet). These must be corrected for distortion.

TABLE III. FRENCH HOSPITAL (HISTORY CHART)

NAME — HISTORY NO. / DR. / X-RAY NUMBER

1. Inlet
   a. Measurement of obstetric conjugate 9.5-11.5 cm.
   b. Measurement of posterior sagittal 4-5 cm.
   c. Measurement of transverse 12-13 cm.
   d. Shape of posterior segment { Gynecoid / Anthropoid / Android / Platypelloid }
   e. Shape of anterior segment { Gynecoid / Anthropoid / Android / Platypelloid }
   f. Symmetry
2. Midplane
   a. Measurement of interspinous diameter 9.5-10.5 cm.
   b. Measurement of posterior sagittal diameter 4.5-5.5 cm.
   c. Prominence of spines.
3. Outlet
   a. Measurement of intertrochanteric diameter 9-11 cm.
   b. Measurement of posterior sagittal of outlet 7.5-9 cm.
4. Depth of Pelvis 90-100 millimeters.
5. Length of sacrum 11-13 cm. { Long / Average / Short }
6. Sacral curve { Straight / Average / Marked }
7. Inclination of sacrum (normal 90°)
8. Width of sacrum { Wide / Average / Narrow }
9. Subpubic angle (normal 80-90°) { Wide / Average / Narrow }
10. Shape of arch { Roman (round) Normal / Gothic (angular) }
11. Sidewalls of pelvis { Converge / Straight / Divergent }
12. Lateral bore { Converge / Straight / Divergent }
13. Apex sacrosciatic notch { Wide / Average (about 3 cm.) / Narrow }
14. Base of sacrosciatic notch wide { Average (4-5 cm.) / Narrow }
15. Baby { Position / Engagement / Flexion / Station / Abnormality }

Therefore, on the lateral plate, the baseline previously described is drawn parallel to the film edge, touching the most lateral border of the sacrum. To determine the distortion of the inlet, the distance from the junction of the posterior and anterior sagittal of the inlet to the baseline is measured, using the ruler image on the plate. Then by simply consulting Table II the true undistorted transverse measurement is given. To correct for the distortion of the midplane, the distance from the midpoint between the spines to the baseline is measured, and again the same table is consulted. For the transverse of the outlet, measure the distance from the midpoint between the tuberosities to the baseline with the ruler image, and then find the corrected transverse measurement on the chart.

2. Architecture of the Pelvis.—While pelvic measurements are important, they do not tell the entire story. The pelvic architecture must be studied very carefully in all three plates. The 45 degree angle exposure is especially valuable in studying the subpubic angle and the side walls (Table III).

Table III is given so that the inexperienced physician may have some system of evaluating the pelvis, and some basis for his judgment of its capacity. A set of average normal measurements are given. If there is any marked variation, it is advisable for the physician to consult with a qualified obstetrician with greater experience, who on the basis of his past experience can better evaluate the pelvic architecture and measurements.

The measurement of the head, or fetal cephalometry, has not been particularly successful in our hands, regardless of the technique used. Communications with other clinics have disclosed similar difficulties.

The reason for the difficulty is clear. First, the frontooccipital is the only diameter that we are able to measure, and this is not the diameter that engages. Next, we compare this with the smallest pelvic diameter and do not take into account the fact that compensatory space may exist either laterally, anteriorly, or posteriorly. Finally, we do not know how much molding the head will undergo as it comes through the pelvic canal. Goodwin's work showing that the long oval head flexes and molds well while the round head does not, definitely contributes toward the solution of this problem. Finally, the mechanism of labor, the condition of the cervix, the intensity of the pains, and many other factors must be considered.

We, therefore, feel that actual measurements of the head may be misleading. If the pelvis is average in measurement with good architecture, a 7- to 8-pound baby should deliver spontaneously. If it is larger, it is capable of accommodating even a larger baby. If it is smaller, a 5- to 7-pound baby will deliver spontaneously. With good pelvic construction, every woman with an average size baby who has an obstetric conjugate of 9 cm. is entitled to the chance of delivery from below. The great majority have no difficulty. We consider an obstetric conjugate of 8 cm. an absolute contraction.

Routine pelvimetry for all primiparas and all multiparas with previous difficult labors will soon be a routine procedure in scientific obstetrics. It is hoped that with the simplification of methods and wider adoption of this procedure, the high incidence of cesarean section will be reduced because of misconceptions concerning the size of the pelvis. We also hope that with this procedure, the abnormal pelvis will be more universally recognized, and adequate measures taken so that proper facilities are available when a difficult delivery is anticipated. When a diagnostic help to the doctor is harmless to the patient, it should absolutely be used whenever possible. If absolute cephalopelvic disproportion is seen, babies will not be subjected to tests of labor which result in birth injuries.

In conclusion, a note of warning must be given. X-ray pelvimetry is not a panacea, but it can be of great value if its limitations are appreciated. It is merely a diagnostic aid. Inexperience is usually

the factor which causes many to make extravagant claims for this procedure. The pelvis is only one factor in labor. The parity of the woman, her race, age, emotional stability, the amount of sedation, the character of the uterine contractions, the dilatation of the cervix, obstructing tumors, the size of the baby, its position, flexion, etc., all are factors which determine the final outcome.

I wish to express my sincere gratitude to Dr. Claude Heaton and Dr. E. M. Claiborne for their help and cooperation in this work.

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115 EAST FIFTY-THIRD STREET

THE NAEGELE PELVIS*

THE OBSERVATION OF THREE CASES AND A COMMENTARY

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ONE hundred and one years ago Franz Carl Naegele[1] gave to the world his celebrated treatise on the obliquely contracted pelvis. Since that time, the name of this particular type of pelvic deformity has memorialized the author of this medical classic, for it is known as "The Naegele Pelvis."

Naegele defined the deformity as a "pelvis contracted in one of the oblique diameters with complete ankylosis of the sacroiliac synchondrosis on one side, combined with imperfect development of the sacrum and os innominatum on the same side." At the time of his writing the author observed that the deformity had never been recognized in the living body. Without the aid of roentgenology, it may be stated that much of the same difficulty of diagnosis that Naegele experienced obtains today, as witnessed by the cases here reported.

The object of the present communication is to place on record the recent observation of three cases and to emphasize the opinion that the deformity probably is not one of the extreme rarity usually assumed. Williams, in 1926,[2] stated that probably less than 100 instances have been described in the literature.

*This study was made possible through the Clinical Research and Teaching Fund of Yale University School of Medicine.

The *first* case presented I have previously recorded,[3] but a brief description is also of interest in this communication. The patient, a woman of 33 years, of Irish descent, gave no history of serious disease in childhood. The menstrual history was negative and no pregnancies had occurred. In 1928 the left kidney was removed in a local hospital, the indication being pyelitis. The removed specimen showed kidney deformity with double pelvis and double ureter. The patient was first seen in the New Haven Hospital the following year. From that time on she has been seen at various intervals, her chief complaint usually being pain in the left lower abdominal quadrant. From 1932 to 1938, 8 pelvic examinations were made by 6 individuals. No note is made following these examinations as to the presence of pelvic deformity. Examinations failed to reveal any definite cause for her discomfort, and in January, 1938, a flat abdominal roentgenogram was made (Fig. 1). The report showed scoliosis of the left dorsal spine and deformity of pelvis with associated sclerosis in region of left sacroiliac articulation; in other words, a Naegele type pelvis. Examination under anesthesia revealed no gynecologic pathology. The external measurements follow:

Interspinous diameter	23.5 cm.
Intercristal diameter	25.0 cm.
Intertrochanteric diameter	29.0 cm.
Right oblique diameter	18.5 cm.
Left oblique diameter	17.25 cm.
External conjugate diameter	17.25 cm.

Pelvic measurements as determined by roentgen pelvimetry:

Anteroposterior diameter of inlet	9.5 cm.
Greatest transverse diameter of inlet	10.0 cm.
Left oblique diameter	11.0 cm.
Right oblique diameter	8.25 cm.
Interischial spinous diameter	6.25 cm.
Intertuberal diameter	10.0 cm.
Posterior sagittal diameter of outlet	5.25 cm.
Height of pelvis	9.25 cm.

Laterally the pelvis showed a male type of sacrosciatic notch, and the sacrum showed an essentially normal curve from above downward on its anterior surface. The pelvic and iliac portions of the terminal length are as follows:

Right side	Pubic portion	6.0 cm.
	Iliac portion	5.5 cm.
Left side	Pubic portion	6.75 cm.
	Iliac portion	4.5 cm.

The external appearance of the patient was not unusual, scoliosis not readily noticeable, and the patient does not walk with any noticeable limp.

The *second* case is that of an Italian woman, aged 38 years, first seen in our clinic in December, 1939. She was then in her fourth pregnancy. Her first pregnancy in 1925 was ended in delivery by forceps in a local hospital of a male child, 7 pounds 10 ounces, now living and well. The second pregnancy in 1928 terminated in spontaneous delivery of a female child, 7 pounds 14 ounces, now living and well. In 1931 she was delivered at home by a local physician of a child which is claimed to have weighed over 8 pounds. This child is said to have suffered a birth injury. It died at the age of thirty-one months from infection, according to the mother's statement.

The patient's past history revealed nothing of importance as far as the pelvic deformity was concerned. Her expected confinement was July 7, 1940. In reviewing this patient's dispensary history, it was found that she visited the clinic in 1934 for "pains in the lower abdomen." At that visit and on four subsequent visits, a vaginal examination was done. These examinations were performed by four different individuals and no mention of pelvic deformity appears on the record. On Dec. 26, 1939, she again presented herself, as noted above, in her fourth pregnancy. At that time a vaginal examination was done by Dr. DeWitt Dominick, who confirmed the

pregnancy and noted that the inferior pelvic strait was abnormal and referred the patient for roentgen pelvimetry. The report of the roentgen examination on Jan. 4, 1940, states that "The pelvic contour is that of a Naegele type with obliquity and deformity on the right" (Fig. 2). The patient's prenatal course was uneventful

Fig. 1.—Case 1. Anteroposterior roentgenogram.

Fig. 2.—Case 2. Anteroposterior roentgenogram.

until she was seen on April 18, 1940, when the relatively large size of the abdomen suggested the presence of multiple pregnancy. Two weeks later this impression was confirmed by roentgen examination. Toward the end of pregnancy the patient's blood pressure began to rise, her weight to increase rapidly, and the urine showed albumin. From May 2 to June 11 the pressure rose from 148/88 to 166/92, and on

June 18 she was admitted to the hospital for observation. Forty-eight hours later the membranes ruptured spontaneously and labor started. She was delivered of male twins without difficulty after a seven-hour labor, and the weight of the children was 2,830 and 2,725 Gm. The puerperium was uneventful and the patient was discharged on the twelfth day post partum. The blood pressure on discharge was 110/82. Before the patient left the hospital roentgen examination of the urinary tract by pyelography was performed. No gross abnormalities were noted. The external measurements of Case 2 follow:

Interspinous diameter	26.0 cm.
Intercristal diameter	29.0 cm.
Intertrochanteric diameter	32.0 cm.
Right oblique diameter	23.0 cm.
Left oblique diameter	19.75 cm.
External conjugate diameter	20.5 cm.

Fig. 3.—Case 3. Anteroposterior roentgenogram.

Pelvic measurements as determined by roentgen pelvimetry:

Anteroposterior diameter of inlet	12.0 cm.
Greatest transverse diameter	10.0 cm.
Left oblique diameter	9.5 cm.
Right oblique diameter	12.4 cm.
Interischial spinous diameter	7.1 cm.
Intertuberal diameter	8.5 cm.
Height of pelvis	9.8 cm.

Laterally the pelvis shows a male type of sacrosciatic notch and the sacrum from above downward shows a slight abnormal displacement forward of the lower half. The pelvic portions of the terminal length are as follows:

Right side	Pubic portion	6.3 cm.
	Iliac portion	8.0 cm.
Left side	Pubic portion	8.3 cm.
	Iliac portion	6.0 cm.

The *third* case, now under observation in our prenatal clinic, is that of a 28-year-old white American who is pregnant for the third time. The first pregnancy in 1935 was terminated in a local hospital by forceps, and a 7.5 pound child delivered,

which is living and well. The second pregnancy ended in the stillbirth of a 9.5 pound infant which was delivered with forceps. The expected date of the present pregnancy is April 4, 1941, and except for some varicosities on both legs and the deformity of the pelvis the pregnancy seems to be uncomplicated.* The past history is of interest because of a history of osteomyelitis during the first three years of life, accounting for numerous scars due to incisional drainage in the region of the left hip.

On her first visit to our clinic on Oct. 1, 1940, she was examined vaginally by my associate, Dr. Clair B. Crampton, who noted that the pelvis presented deformity and he referred the patient for roentgen pelvimetry. The roentgen findings showed the presence of a typical Naegele pelvis with the deformity on the right side (Fig. 3). The external measurements were as follows:

Interspinous diameter	22.5 cm.
Intercristal diameter	24.25 cm.
Intertrochanteric diameter	29.0 cm.
Right oblique diameter	17.75 cm.
Left oblique diameter	15.0 cm.
External conjugate	17.5 cm.

Pelvic measurements as determined by roentgen pelvimetry:

Anteroposterior diameter of inlet	11.0 cm.
Greatest transverse diameter of inlet	10.0 cm.
Left oblique diameter	9.4 cm.
Right oblique diameter	11.8 cm.
Interischial spinous diameter	8.1 cm.
Intertuberal diameter	8.2 cm.
Posterior sagittal diameter of outlet	9.0 cm.
Height of pelvis	9.25 cm.

In addition to the roentgenometric findings, the films showed some destruction of the crest of the ilium on the left or the side opposite to the pelvic deformity. This destruction is characteristic of that caused by osteomyelitic disease.

Laterally the pelvis showed a femal type of sacrosciatic notch, and the sacrum was convex from above downward on its anterior surface, somewhat characteristic of the rachitic sacrum. The pelvic and iliac portions of terminal length were as follows:

Right side	Pubic portion	6.5 cm.
	Iliac portion	5.5 cm.
Left side	Pubic portion	6.3 cm.
	Iliac portion	7.0 cm.

Except for the scars on the left side, the external appearance of the patient is not unusual and the scoliosis is not marked. The patient does not walk with a noticeable limp.

COMMENT

In discussing the origin of this type of pelvic deformity Naegele wrote, "I confess that my original opinion about it, namely that the deformity originates neither from external force nor from disease but by a deviation in the original development, appears the most probable." Naegele gave his reasons for this opinion, which I quote in part as follows:

"The intimate and complete fusion of the os sacrum and os ilium includes the inner structure of the bones as well as its external appearance. There is no trace of growing together of formerly separated parts in the region of the synostosis. . . . The os sacrum and os innominatum form one bone . . . if our fusion of the os

*This patient was delivered by cesarean section, March 28, 1941. The child weighed 3,890 Gm.

sacrum and os ilium should be considered as a synostosis acquisita as a consequence of inflammation or of pressure, etc., it could hardly be found as complete, as uniform as we find it in all pelves of our class. . . . The truly striking resemblance of these pelves to one another in all important characteristics is so obvious. . . . Whoever has seen a series of such specimens must have the idea that there is a common cause for this deformity. Does not identity of the effect speak for the identity of the cause? . . . In none of the cases could a disease or an exterior force be made responsible for the deformity. All cases which have come to my knowledge occurred in young people who had previously been healthy.''

However, in spite of Naegele's impressive argument, Thomas of Leyden,[4] in 1860, stated that in certain cases inflammatory disease rather than congenital defect was responsible for the condition. At a later date Breus and Kolisko[5] went further and stated that the condition was always the result of inflammatory disease and that the history and presence of cicatrices would substantiate this fact. In 1929, Williams[6] concluded that this latter opinion may not apply to the individual case. In his case, as in Reinberger's[7] reported in 1933, an embryonic defect was the only solution that explained the deformity. In addition to the pelvic deformity in the latter's case, there were deformities of the lower extremities and supernumerary digits of both upper and lower extremities, and the genital tract showed a uterus septus with double cervix and double vagina.

In 1917, Berry Hart[8] summarized his views on this subject as follows: ''The true Naegele and Robert pelves have not had a previous ostitis with resulting ankylosis in the region of the sacroiliac joints, followed by disturbed weight transmission. The pseudo-Naegele and pseudo-Robert pelves have had a previous ostitis in these regions, and there the synostosis and atrophy are the result of this. The forms of the Naegele and Robert pelves are the result of polar losses of the size elements of the alae sacri and innominate bones, due to maturation of the sperm- and germ-cells. In these the loss of the alae sacri and innominate determinants has occurred, a great rarity, more often a unilateral loss (Naegele) than a bilateral one (Robert). The sacroiliac ankylosis is due to the fact that by such losses (bony elements and joint elements) the part remaining, imperfectly developing, becomes ankylosed. As this is a germ-plasma change, and multiplication of the reduced elements occurs, it may be transmitted.''

It is of interest to note that Bluntschli[9] in 1911 described the occurrence of this type of pelvic deformity in the monkey *(Macacus cynomolgus)* and that earlier in 1878 Thomson[10] exhibited the skeleton of a wombat (Phascolomys) in which the same unilateral sacral changes were present.

The association of this deformity with evidences of maldevelopment in other parts of the same individual certainly gives some weight to the congenital nature of its origin. In Case 1 of the present group, in Reinberger's case, and in Riviere and Riviere's case, the coexistent malformations were those definitely associated with the urogenital system. In the latter instance reported in 1923,[11] there was absence of the half of the uterus, uterine horn, and ovary, all on the same side as the bony deformity. A recent personal communication from Dr. N. J. Eastman reports a case of Naegele pelvis in a patient in whom nephrectomy was performed for renal tuberculosis, occurring on the same side as that of the deformity.

The diagnosis of Naegele pelvis in the living being presents an interesting topic for discussion. In many instances, as in the cases here presented, knowledge of the condition is unknown until for one reason or another a roentgenogram of the pelvis is made. In my first case and in Dr. Eastman's case, the deformity was discovered during a urologic investigation. In the second and third cases of the present group, both individuals had given birth to children and had been subjected to numerous vaginal examinations by presumably competent observers before

the true condition was suspected. With regard to these examinations it is fair to state that only within a comparative recent time has our attention been specifically directed to the obstetric importance of midplane contractions. In any event, it is obvious that the diagnosis may not be readily apparent without the use of roentgen investigation.

The absence of obvious external deformity and change in gait are also contributory to the obscurity of diagnosis. However, variations in the height of the iliac crests and an accompanying scoliosis are suggestive findings. The transverse diameter of the outlet is always diminished, usually markedly, so that there is a definite sense of constriction in examining vaginally. Laterally the pelvic side wall on the affected side is readily felt on vaginal examination and is found to be displaced toward the body midline. A simple anteroposterior roentgenogram always settles the diagnosis.

CONCLUSION

The finding of three Naegele pelves within two years in the relatively small material of our clinic suggests that this type of pelvis may not be one of extreme rarity. The history of full-term pregnancies successfully delivered in the second and third case also suggests that such a pelvis may easily remain unrecognized in the ordinary course of events. The potential difficulties which may result obstetrically in such pelves point out the importance of a definite diagnosis in each case. The importance of the routine procedure which we have carried out for the past six years, namely that of performing roentgen pelvimetry on every primigravid woman, again becomes obvious.

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There were 74 patients under 16 years of age among 133,361 deliveries during the years 1931 to 1938 in 23 municipal maternity units in London, England. The maternal mortality was nil, and there were 2 stillbirths and 3 neonatal deaths. The labors were, with few exceptions, short and unusually easy. There was a slight increase over the normal rate for these hospitals of forceps, surgical inductions, and puerperal morbidity. Complications, especially during the third stage, were rare. There was no evidence that maternity had produced excessive nervous or mental strain, and no case of mental or nervous breakdown has been traced.

Carl P. Huber.

PROLAPSE OF THE UMBILICAL CORD

Analysis of One Hundred and Fifty-Five Cases

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ANALYSIS of 155 cases of cord prolapse occurring at the Providence Lying-in Hospital during the fifteen years preceding July 1, 1940, brings out several facts at variance with accepted concepts. For the sake of brevity, the essential statistics of this review will be presented in tabular form, and only points of particular interest will be discussed.

INCIDENCE

Cord prolapse occurred 155 times in 36,773 consecutive viable confinements, an incidence of 0.42 per cent. Comparison of this figure with others (Table I) suggests that a general reduction in the incidence of this mishap is taking place.

Table I. Incidence of Cord Prolapse

YEAR	SOURCE OF FIGURES	CONFINEMENTS	PROLAPSED CORDS	INCIDENCE PER CENT
1907 to 1922	Review of 8 reports, by Kurzrock[1]	260,437	2,408	0.92 Ave.
	Highest incidence in above			1.18
	Lowest incidence in above			0.53
1932	Kurzrock's series[1]	16,942	100	0.59
1940	Mengert and Longwell[2]	9,546	63	0.66
	Draa[3]	5,035	18	0.35
	Hillis[4]	9,581	25	0.26
	Providence Lying-in Hospital	36,773	155	0.42
	Composite figures for 1940	60,935	261	0.43 Ave.

The average incidence of 0.44 per cent for reports made in 1940 represents more than a 50 per cent reduction from that of 0.92 per cent computed from figures published between 1907 and 1922.

ETIOLOGY

Of the possible predisposing conditions analyzed in Table II, the abnormal pelvis and parity warrant brief discussion.

Whereas the standard textbooks[5, 6] state that contraction is the principal bony anomaly predisposing to cord prolapse, one-half of the abnormal pelves in this series were of the justo major type. The remaining half included 4 flat and 3 generally contracted pelves, 2 android pelves and 2 gynecoid with narrow forepelves, 2 pelves with prominent sacra and 1 with protruding promontory. The following case illustrates the role an abnormal pelvis can play in prolapse of the cord.

Case 1.—(Unit No. 31,236.) A 40-year-old primigravida with a small male pelvis by clinical examination was to have a trial labor, with cesarean section held in

TABLE II. POSSIBLE PREDISPOSING FACTORS IN 155 CASES OF CORD PROLAPSE

POSSIBLE PREDISPOSING FACTOR	NO.	INCIDENCE PER CENT	FETAL MORTALITY	
			DIED	PER CENT
Abnormal bony pelves	28	18.1	13	46.4
Abnormal placentations	9	5.8	7	77.7
Polyhydramnion	9	5.8	5	55.5
Infants over 9 pounds birthweight	24	15.5	15	62.5
Infants under 6 pounds birthweight	34	21.9	21	61.8
Premature infants	32	20.6	23	71.7
Twins	10	6.5	2	20.0
Abnormal fetus, hydrocephalic	1	0.7	1	100.0
Abnormal lies and presentations	61	39.4	28	46.0
Transverse lies	13	8.4	7	53.8
Longitudinal lies	48	30.9	21	43.7
Cephalic presentations	11	7.2	7	63.6
Compound	9	5.8	6	66.7
Face	2	1.3	1	50.0
Sacral presentations	37	23.9	14	37.8
Double footlings	18	11.6	8	44.4
Single footlings	14	9.0	4	28.6
Full breeches	2	1.3	1	50.0
Frank breech	1	0.7	0	0.0
Unclassified	2	1.3	1	50.0

Overlapping exists in the above groups, and conversely some cases fall into no group. Fifty-seven occipitoanterior and 37 occipitoposterior positions, with fetal mortalities of 57.7 and 43.2 per cent, respectively, are not included in this table; nor are parity figures, cited in the text.

reserve as a possible eventuality. During the first stage of labor, while the head was unengaged, the fetal heart tones disappeared. Eleven hours later she delivered a stillborn fetus with a prolapsed cord. She was pregnant again the following year, and bore a fetus larger than her first. Stereoroentgenologic examination near term disclosed an android pelvis with a high posterior vertex. After two hours of labor, while the head was still unengaged and the cervix dilated only 2 cm., the fetal heart tones became irregular. The patient was placed in the Trendelenburg position, prepared, and delivered by the abdominal route. When the uterus was opened, the umbilical cord was found "below the head, compressed against the brim of the pelvis." A living 8 pound 2 ounce infant was obtained.

Multiparity is commonly said to favor cord prolapse.[5, 6] This study embraces 14,181 primiparous and 22,592 multiparous confinements, of which 58 and 97, respectively, were complicated by prolapse of the cord. The percentage incidence of cord prolapse in these two groups, 0.41 for primiparas and 0.43 for multiparas, discounts at least in this study the etiologic importance of multiparity. Furthermore, the fetal mortality percentages, 51.7 and 48.5, respectively, are of almost identical order.

Table III, which analyzes the precipitating causes of cord prolapse, reveals that any pelvic manipulation or even the patient's struggles under anesthesia may act as an initiating factor. Artificial rupture of the membranes was performed in 27 cases with living infants on the following indications: prolonged labor 12, induction of labor 7, control of hemorrhage 4, and to expedite delivery of the second twin 4. Insertion of a Voorhees' bag initiated cord prolapse once, while its expulsion was followed by the mishap 4 times. Manual rotation of the head pre-

TABLE III. PRECIPITATING FACTORS IN 85 CASES OF CORD PROLAPSE

PRECIPITATING FACTOR	NO.	INCIDENCE PER CENT	FETAL MORTALITY	
			DIED	PER CENT
Spontaneous				
Rupture of membranes	27	17.4	18	66.7
Straining at stool	1	0.7	1	100.0
Accidental				
Rectal examination	1	0.7	1	100.0
Vaginal examination	3	1.9	1	33.3
Anesthesia (second stage gas-oxygen)	1	0.7	1	100.0
Artificial rupture of membranes	29	18.7	8	27.6
Corrected by deduction of two toxic cases with dead infants	27	17.4	6	22.2
Voorhees' bag	5	3.2	5	100.0
Dührssen's incisions	1	0.7	1	100.0
Manual rotation of head	10	6.5	6	60.0
Midforceps delivery	2	1.3	1	50.0
High forceps delivery	3	1.9	3	100.0
Internal podalic version	1	0.7	1	100.0
Internal cephalic version	1	0.7	0	0.0

cipitated prolapse in 10 cases. Adherence to stricter qualifications for the performance of these procedures is seen as an important factor in the diminishing incidence of cord prolapse previously noted.

MANAGEMENT

The management of these cases was shared by 18 physicians attending private patients, and numerous residents under the supervision of

TABLE IV. INDIVIDUAL METHODS OF MANAGEMENT EMPLOYED IN 155 CASES OF CORD PROLAPSE

METHOD OF MANAGEMENT	NO.	FETAL MORTALITY	
		DIED	PER CENT
Spontaneous delivery	17	14	82.3
Postural treatment	20	5	25.0
Manual elevation of presenting part	1	0	0.0
Cord replacement			
Successful	3	1	33.3
Unsuccessful	12	6	50.0
Artificial rupture of membranes			
For forelying cord	5	1	20.0
For occult prolapse	3	0	0.0
Cervical tamponade	1	1	100.0
Dührssen's incisions	2	2	100.0
Voorhees' bag	4	4	100.0
Manual dilatation of cervix	14	9	64.3
Manual rotation of head	11	5	45.4
Forceps extraction			
Low	15	8	53.3
Mid	26	11	42.3
High	12	11	91.7
Breech extraction	31	13	41.9
Braxton Hicks' version	2	2	100.0
Version and extraction	52	25	48.1
Cesarean section	4	0	0.0
Craniotomy	2	2	100.0

More than one of the above procedures was employed in many cases. Note the mortality figures associated with operations directed at opening the cervix.

the attending staff. Table IV summarizes the individual methods employed. It may be stated that temporizing measures, especially postural treatment, prefaced the successful outcome of many cases with incompletely dilated cervices; that efforts to open artificially the partially dilated cervix were, with the occasional exception of manual dilatation, uniformly unsuccessful; and that cases where immediate delivery through the completely dilated cervix was feasible were generally successful within the limits imposed by concomitant obstetric pathology.

Table V abstracts 51 successfully managed cases where cervical dilatation and station of the presenting part at the time of cord prolapse were

TABLE V. FIFTY-ONE SUCCESSFULLY MANAGED CASES OF CORD PROLAPSE WHERE CERVICAL DILATATION AND STATION AT THE TIME OF PROLAPSE WERE RECORDED

STATION	CERVIX	NO.	MANAGEMENT
High	2 cm.	1	Cesarean section
		1	Postural; cesarean section
	4 cm.	2	Postural; cesarean section
		1	Postural; artificial rupture of membranes; version and extraction
		1	Postural; artificial rupture of membranes; low forceps
	6 cm.	1	Postural; spontaneous delivery
		1	Manual dilatation of cervix; version and extraction
		1	Version and extraction
		1	Postural; low forceps
	8 cm.	2	Version and extraction
		1	Failed high forceps; version and extraction
		1	Manual dilatation of cervix; high forceps
	Compl.	4	Version and extraction
		1	Artificial rupture of membranes; version and extraction
		1	Postural; version and extraction
Mid	4 cm.	1	Artificial rupture of membranes; version and extraction
		1	Manual dilatation of cervix; breech extraction
		1	Postural; breech extraction
	6 cm.	1	Manual dilatation of cervix; breech extraction
		1	Manual rotation of head; midforceps
		1	Postural; breech extraction
	8 cm.	2	Manual rotation of head; midforceps
		1	Unsuccessful attempt at replacement; manual rotation of head; midforceps
		1	Failed midforceps; version and extraction
	Compl.	4	Version and extraction
		4	Midforceps
		1	Manual elevation of head; version and extraction
		1	Midforceps rotation and extraction
		1	Artificial rupture of membranes; manual rotation of head; midforceps
		1	Breech extraction
Low	6 cm.	2	Low forceps
	Compl.	3	Low forceps
		3	Breech extraction
		1	Spontaneous delivery

In the above cases, a time factor during which the cord was not fatally compressed frequently intervened between cord prolapse and ultimate delivery. Temporizing measures prolonged this time factor in many instances.

recorded. Scrutiny of these cases further emphasizes the fundamental importance of postural treatment. The author personally managed the following case which afforded opportunity to evaluate its efficacy.

CASE 2.—(Unit No. 35,396.) A multipara was admitted to the hospital in active labor with a hand, foot, and cord protruding through a cervix dilated 5 cm. The fetal heart tones became slow and slightly irregular with the patient in the horizontal position, and consistently returned to normal when she was placed in deep Trendelenburg. Except for three experimental periods when she was horizontal, the patient was maintained in Trendelenburg position for more than four hours, during which she experienced normal labor pains. Eventually the cord appeared at the introitus, and was becoming pulseless. Examination showed the cervix to be adequate, and a living child was delivered by version and extraction.

Four patients, each with cord prolapse occurring through a cervix less than one-half dilated, were successfully delivered by cesarean section. One abdominal delivery (Case 1) has already been described; the two following cases are of special interest:

CASE 3.—(Unit No. 15,328.) Prolapse of the cord occurred immediately after spontaneous rupture of the membranes in a 32-year-old multipara who was not in labor. Six hours later, still not in labor, she was admitted to the hospital with a loop of strongly pulsating cord hanging from the introitus. Cesarean section with removal of the prolapsed cord from below saved the infant's life.

CASE 4.—(Unit No. 35,203.) Artificial rupture of the membranes to induce labor precipitated prolapse of the cord in a 41-year-old toxic primigravida. She was placed in the knee-chest position while arrangements for operation were made, and in the Trendelenburg position while being prepared for operation. A 9-pound infant was delivered successfully by the abdominal route.

Since conservative treatment would almost certainly have condemned these infants, it is felt that cord prolapse in the absence of active labor, with both mother and fetus in good condition, constitutes a strong argument for cesarean section.

MORTALITY AND MORBIDITY

The mortality and morbidity statistics for this series appear in Table VI. Infant mortality lies within the generally accepted figures for cord prolapse. Subtraction of 22 cases where the fetus was considered dead on admission yields a 40.7 per cent fetal mortality for "treatable" cases. Infant morbidity assumes a substantial figure; of 78 living infants discharged from the hospital, 7 left with clinical evidence of more or less

TABLE VI. MORTALITY AND MORBIDITY STATISTICS

MORTALITY	NO.	PER CENT
Fetal deaths in 155 cases	77	49.7
Corrected for 1 neonatal death due to hemorrhagic disease of the newborn	76	49.0
Fetal deaths in 133 "treatable" cases	54	40.6
Maternal deaths	0	0.0
MORBIDITY		
Living infants discharged with birth injuries (total discharged living, 78)	7	9.0
Morbid puerperiums	24	15.6

serious birth injury: 3 with brachial plexus paralyses, 2 with intracranial hemorrhage, 1 with facial paralysis, and 1 with a cephalematoma.

There were no maternal deaths, and 24, or 15.6 per cent, of the parturients experienced morbid puerperiums.

SUMMARY AND CONCLUSIONS

1. One hundred and fifty-five cases of cord prolapse occurred in 36,773 consecutive confinements with viable children at the Providence Lying-in Hospital, an incidence of 0.42 per cent. Comparison with other figures suggests that the incidence of cord prolapse is decreasing.

2. Of possible predisposing conditions the justo major pelvis assumed an importance equal to the contracted pelvis in this series. Multiparity played a minor, if any, causative role.

3. The commoner accidental causes of cord prolapse were artificial rupture of the membranes, the use of Voorhees' bag, and manual rotation of the head. It is felt that diminishing use of these procedures contributes to the diminishing incidence of cord prolapse.

4. Aside from pathologic conditions frequently associated with cord prolapse, the main obstacle to successful management was the partially dilated cervix. In these cases temporizing measures, especially postural treatment, were often successful in obviating pressure on the cord until delivery could be effected. Artificial methods of opening the cervix were for the most part unsuccessful.

5. Prolapse of the cord before the onset of labor, with both mother and fetus in good condition, presents a strong argument for cesarean section.

6. Infant mortality was 49.7 per cent, and 9 per cent of the living infants discharged from the hospital might be considered morbid. Maternal morbidity was 15.6 per cent; there were no maternal deaths.

I desire to express my gratitude to Dr. Bertram H. Buxton, Chief of Staff at the Providence Lying-in Hospital, for permission to review and present this series of cases.

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ANOXIA FOLLOWING NITROUS OXIDE ANESTHESIA FOR LABOR*

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COMPLICATIONS following nitrous oxide anesthesia have been known since this gas was first introduced as an anesthetic into surgery almost one hundred years ago. That death may occur during the administration of this anesthesia for minor procedures such as extraction of a tooth, is common knowledge. However, the occurrence of delayed deaths, the development of pathologic personalities, and other varied clinical pictures of organic brain disease caused by the use of nitrous oxide anesthesia have been reported only in the past few years.[1, 2, 4, 5, 8-10] The anoxemia accompanying nitrous oxide anesthesia, either alone or combined with the effects of certain preoperative medication, has been shown to produce asphyxia of the brain cells or cerebral anoxia with its resulting necrosis of brain tissue.

Our interest in the potential danger of damage to the central nervous system caused by nitrous oxide was aroused by a recent experience in which a patient developed serious signs of diffuse brain damage when this anesthetic was used in the last stages of labor. To those who practice obstetrics, a field in which nitrous oxide anesthesia is so commonly employed, a discussion and survey of the literature is worthy of emphasis, especially since all the pertinent literature on maternal anoxia has been published in surgical, medical, or neuropsychiatric bulletins, and none was encountered in obstetric journals.†

Caine,[5] in 1923, was the first to publish the records of 4 patients who manifested severe delayed cerebral changes, but it remained for Courville,[1] in 1936, to establish clearly the pathogenesis of cerebral anoxia following nitrous oxide anesthesia. Since his original excellent monograph, to which he has made valuable additions, there have been an increasing number of cases reported. To these we wish to add the following example of post-anesthetic encephalopathy with delayed death.

CASE REPORT

A. C., colored female, aged 31 years, para iv, gravida v, was admitted to the Obstetrical Ward Service of The Brooklyn Hospital June 30, 1940, with ruptured fetal membranes and irregular uterine pains. There was a normal prenatal course. The blood Wassermann test was negative and the blood pressure, urinalysis, and gain in weight were all within normal limits.

The previous deliveries were all uneventful, except for the third baby, which died at birth from an unknown cause. At The Brooklyn Hospital five and one-half years ago during the second stage of delivery of the fourth and last baby, gas oxygen anesthesia was administered without ill effects.

On examination, the patient showed no evidence of toxemia and was in good health, with normal heart and lungs. By rectal examination the uterine cervix was

*Presented at a meeting of the Brooklyn Gynecological Society, December 6, 1940.

†Careful study has been given to the problem of anoxia in the newborn infant by Eastman, Clifford, and others in contributions published in this JOURNAL and elsewhere, while the subject of mental deficiency in later life has been taken up by Schreiber, of Detroit (Proc. Am. A. Ment. Deficiency 63: 95, 1939).

soft, thick, and undilated. The fetus was estimated to be larger than average, and the fetal vertex was movable over the brim of the pelvis; the fetal heart was regular, 132 per minute.

Eleven hours after admission strong uterine contractions occurred regularly at five-minute intervals. Vaginal examination at this time revealed the uterine cervix dilated to admit two fingers and still thick. The vertex was still above the brim of the pelvis and no forewater was palpated.

At the end of twenty-four hours of labor, the cervix was found dilated to admit three and one-half fingers, and the vertex was fixed in the pelvic brim. Twenty-eight hours after the onset of labor, the patient experienced during the second stage of labor unusually severe labor pains, for the relief of which gas-oxygen was administered with each uterine contraction. The vertex crowned in the transverse position where its further progress was arrested. At this point, meconium was noticed coming from the vagina and the nurse reported that the fetal heartbeat, audible two minutes before, no longer could be heard. Ether was added to the gas-oxygen mixture to induce complete anesthesia. After rotating the head on the perineum, delivery of the fetus was accomplished easily with the aid of forceps. The baby was stillborn and weighed 11 pounds 8 ounces.

As the head was being delivered with forceps and while the patient was still under the influence of the anesthetic, the patient's respirations became irregular, shallow, and slowed to less than eight per minute. The pulse of poor quality became momentarily imperceptible, and then quickened to 144 per minute. Twenty minutes after the continuous administration of pure oxygen, intermittent injections of coramine, adrenalin, and intravenous (50 per cent) glucose, there was an improvement in the pulse and respiratory rate; the blood pressure reading was 160 systolic and 100 diastolic; but her general condition remained poor.

During the first stage of labor and prior to the administration of gas-oxygen, the patient was given two combined doses of $\frac{1}{8}$ gr. of morphine sulphate and $\frac{1}{200}$ gr. of scopolamine; and three doses of $\frac{1}{8}$ gr. of morphine sulphate, the last of these one and one-quarter hours before delivery.

The total duration of labor was twenty-eight hours and nine minutes, the first stage lasting twenty-seven hours and forty minutes, the second stage, twenty-three minutes, and the third stage, six minutes.

Approximately one hour following delivery of the fetus, there occurred muscular twitchings of the face, first involving the left and later both sides, extreme restlessness and unintelligible jabbering sounds. The eyes remained open and staring, the pupils were dilated, and the lower extremities were spastic.

Five hours after delivery the upper extremities became rigid. The patient tossed her head from side to side, cried out loudly, and thrashed around so much that restraint was necessary. The facial grimaces continued. She perspired a great deal and salivated considerably.

The patient cried out to painful stimuli about the face, but no movement of the arms or legs occurred. An examination of the cerebrospinal fluid twelve hours later showed 5 lymphocytes per c.mm. and a normal pressure.

The clinical picture forty-eight hours later was that of widespread decortication. All four extremities were paralyzed, a bilateral extensor toe sign being elicited. There was little movement about the mouth. The patient was unable to swallow and tube feeding was instituted. The optic fundi were normal. The patient cried out, was extremely irrational, and was incontinent.

The blood pressure rose to 190 systolic and 120 diastolic.

At the end of the first week, there occurred spasms of hyperpronation and adduction of the arms, with extension of both legs and conjugate deviation of the eyes in either direction. No attention was paid to her surroundings. The patient seemed completely devoid of intellect and to be purely vegetating.

At the end of the first month the patient answered questions, swallowed fluids, but generally remained out of contact with her environment, and was continuously incontinent. The lower extremities remained paralyzed, there was a fair amount of movement in the right arm and a trace of movement in the left arm. The muscle tone was increased throughout.

During the remainder of her stay in The Brooklyn Hospital, the mental and physical status remained unchanged. There was no fever except for a brief period caused by uterine infection. The blood pressure, normal on admission, remained consistently high, ranging around 190 to 210 systolic and 120 to 140 diastolic.

The patient was transferred to the Kings County Hospital where her condition gradually became worse until death occurred on Oct. 19, 1940, three and one-half months after the anoxic episode. A post-mortem examination was performed by the medical examiner. Grossly scattered minute areas of necrosis were found in the gray and white matter of the cortex and the gray matter of the base of the brain.

Brain.—Externally, the brain showed very little, but was very pale. No particular lesion was noted. The brain had already been cut horizontally in one section. In the fresh state, scattered discoloration of the gray matter of the cortex was seen. The surface was considerably shriveled. Fresh sections in the horizontal plane showed the following:

Widely disseminated, apparently degenerative lesions, involving the gray matter of the cortex with a striking tendency to involve the deepest layers of the cortex in laminar fashion. The most severe changes were in the occipital and parietooccipital regions where actual necrosis was observed and where the cortex was more extensively involved.

Elsewhere the lesions were granular and translucent. The area striata was grossly intact for the most part. On the right side there appeared to be a few similar lesions.

The section was through the superior part of the caudate which showed a few scattered grayish translucent spots of a similar type. The basal ganglia were less severely affected than the cortex. There were a few scattered grayish translucent areas (1 to 2 mm. in diameter) in ganglia. Most areas of the cortex seemed to be involved, at least in part, but not all areas.

One block through the parietooccipital region involving area of necrosis.

Other sections of the hemisphere revealed the same pathology.

The dentate nucleus (left) also has a granular appearance.

Brain stem showed no significant change. Olives were normal.

DISCUSSION

Nitrous oxide is thought to be the safest anesthetic for short operations. It is pleasant to take, causes no iritation, produces little excitement, and is supposedly free from aftereffect. Anesthesia from nitrous oxide is produced largely by exclusion of oxygen and partly by a direct narcotic action of the gas on the brain cells. Hence, the depth of anesthesia depends more upon the reduction of oxygen than upon the increased concentration of nitrous oxide.[1, 6, 7]

The respiratory disturbances, convulsive features, and cyanosis produced by undiluted nitrous oxide are purely asphyxial or are associated with a state of anoxia, and, in practice, this state of asphyxia is prevented from reaching serious proportions by the addition of oxygen.[7] However, to obtain successful surgical anesthesia it is necessary to administer 80 per cent to 95 per cent concentration of nitrous oxide,[4] since anesthesia with this gas cannot be produced unless it is accompanied by some anoxemia. In the presence of ample oxygen where anoxemia could play no part, Brown, Easson and others[6] were unable to produce anesthesia in experimental animals. McClure and his co-workers[4] state that "Nitrous oxide-oxygen anesthesia of complete grade requires the reduction of the oxygen in the inspired mixture below maintenance levels (about 6 per cent), therefore, pure nitrous oxide anesthesia predicates anoxic anoxia." This is a dangerous small factor of safety when it is recognized that high concentrations of nitrous oxide are capable of producing brain damage.

There are four types of asphyxia or anoxia described, anoxic, anemic, stagnant, and histotoxic.[4, 12] It is believed that a combination of all or several of these types results in serious complications.

The first type, anoxic anoxia, results from reduced arterial oxygen and depression of the respiratory center. In addition anything which will interfere with the respiratory mechanism such as disease of the lungs, or their accessory components, by diminishing the amount of oxygen inspired, will add to the danger of anoxia.

The second type, anemic anoxia, is due to a lack of, or inactivation of, hemoglobin, decreasing its capacity to take up oxygen. The third type, stagnant anoxia, results from retardation of the circulation which interferes with the transportation of oxygen.

The last type, histotoxic anoxia, is caused by drugging of the tissue cells so that they cannot utilize the available oxygen.

The following case reported by McClure and others[4] illustrates all the above types of anoxia with fatality.

A white, unmarried female, with bilateral pulmonary tuberculosis and secondary anemia, was treated by pneumothorax. The last pneumothorax was performed July 14, 1938, when 375 c.c. of air was introduced into the left pleural space. Adenoidectomy was performed July 15, 1938, with 1½ gr. of nembutal, ⅙ gr. of morphine sulphate, and $\frac{1}{200}$ gr. of atropine as preoperative medication, and nitrous oxide-oxygen anesthesia. The anesthesia lasted only twenty minutes, but obvious cyanosis persisted throughout. The patient's condition was satisfactory when she was returned to her room an hour later, but she was still unconscious and cyanotic. One hour later respirations became labored and soon stopped. *Anatomic Diagnosis:* Asphyxia, blood uncoagulable; fibrocaseose tuberculosis; bilateral, chronic salpingitis. In this case the pneumothorax twenty-four hours previously and the nitrous oxide would account for anoxic anoxia; the secondary anemia for anemic anoxia; the surgical procedure for the low blood pressure and stagnant anoxia; and the preoperative medication, nembutal and morphine for histotoxic anoxia.

Preoperative medication, principally morphine and the barbiturate derivatives, is capable of producing anoxia if used in moderate to large doses.[4] Thus, the preoperative use of a barbiturate medication in large doses has been considered responsible for the only case of encephalopathy from cyclopropane in the literature.[3] This is quite significant since cyclopropane has been heralded as an excellent anesthetic because of the high percentage of oxygen (77 per cent or more) reaching the patient during its administration.[4] The barbiturates and morphine are respiratory and circulatory depressants, and, therefore, can add to the anoxic anoxia of anesthesia those of the histotoxic and stagnant types. In fact barbiturates alone if used in large doses can produce cerebral necrosis in both human beings and experimental animals.[4] For this reason it would seem wise to use only the short-acting barbiturates in smaller doses as a preoperative medication. Many of the narcotics and anesthetics commonly used are capable of producing anoxia in some degree, although not enough to cause serious consequences. Should transitory failure of respiration and circulatory depression supervene, then asphyxia of the cortical cells takes place.[1]

Other factors which may be responsible for anoxia have been traced to faulty gas machines, impurities of the gas, alcoholism on the part of the patient, or to the unskilled anesthetist.[1, 4]

The clinical picture caused by nitrous oxide asphyxia is bizarre, although certain features are fairly constant. In some of the cases reported, the patients died in respiratory failure while still on the table; others who recovered from a temporary cardiorespiratory failure developed delayed symptoms soon after returning to their rooms, and still others whose behavior during the anesthetic was apparently satisfactory, likewise, developed symptoms as late as hours or days after operation. Cardiorespiratory failure on the table, so commonly reported in itself, adds to the anoxia produced by the anesthetic and preoperative medication. Cyanosis during the anesthesia may or may not be present, and is not necessarily an index of the degree of anoxemia. In several of Courville's fatal cases, cyanosis was notably absent.

The patient may never react from the anesthetic, but remain comatose. Muscular twitchings varying from mild restlessness to severe convulsions, decortication phenomena or rigidity, and hyperthermia are all indicative of cerebral damage.[9] Death may follow after a variable interval. Those who survive are mentally confused and manifest athetoid movements and visual disturbances. Undoubtedly, many minor transient cases recover unrecognized.

These symptoms are better understood in the light of the observations at autopsy which vary with the period of survival, and resemble closely the changes noted in patients dying from carbon monoxide poisoning and acute alcoholism. Courville[1, 2] and McClure's group[4] have recorded their necropsy findings in detail.

In patients dying within twenty-four hours, the gross examination revealed engorgement of the pial and cerebral blood vessels. The lungs were voluminous and of increased density as a result of edema and congestion. Microscopically, the essential changes in the brain were pericellular and perivascular edema, shrinkage of the pyramidal cells of the cortex and other ganglion cells; and cuff hemorrhages especially in the basal nuclei. In the lungs, hemorrhagic infiltration (hemorrhagic pneumonia) was present. Small hemorrhages were occasionally seen in the cortex of the adrenal glands and kidneys.

When death followed after an interval of two days or more, areas of hemorrhage and necrosis were observed in addition to all the above changes. While in some instances the necrosis was limited to focal areas in the cortex, in others, the entire lobes were involved. The individual cells were seen in stages of liquefaction, lipiodol degeneration, and calcification. The lungs either showed resolution of the hemorrhagic pneumonia of the acute phase, or had progressed to frank consolidation of lobular distribution. Hemorrhage and tubular degeneration were present in the kidneys.

CONCLUSIONS

1. Anoxemia accompanying nitrous oxide anesthesia, either alone or combined with the effects of certain preoperative medication, has been shown to produce asphyxia of the brain cells or cerebral anoxia with its resulting necrosis of brain tissue.

2. The dangers of nitrous oxide anesthesia as a cause of delayed deaths, pathologic personalities, and other varied clinical pictures of organic brain disease are emphasized to those who practice obstetrics.

3. The case history of a patient who developed severe brain damage following nitrous oxide anesthesia for labor and died three and one-half months later is reported.

4. The pathologic observations reported in the literature are summarized.

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DISCUSSION

DR. HAROLD R. MERWARTH.—Attention has been called to this condition only since 1923 and especially since 1936, when the work of Courville of California appeared.

The clinical picture in the case presented was essentially that of widespread decortication. The patient suffered both visual and auditory hallucinations, was virtually completely paralyzed, had to be tube-fed, and was continuously incontinent.

An interesting point which was not emphasized in the history was the fact that at no time did the blood pressure drop below 190 or 200 points. This was probably explained by the autopsy findings in the left kidney which was completely eliminated by infarcts. There was also damage to the right kidney and other changes in the lungs. The brain was disappointing on gross examination and on cutting required careful inspection to find the damage done. This was essentially limited to the gray matter of the cortex and lenticular nucleus, involving chiefly the innermost cells of the gray matter of the frontal, occipital, and temporal lobes. There also was damage to the dentate nucleus of the cerebellum. The changes noted in this specimen are not found characteristically in carbon monoxide poisoning, but would account for the mental symptoms in the case.

Had the patient survived, the resulting damage would have been such that she would always have manifested symptoms of a chronic deterioration of the brain in the form of a paralysis agitans or tremors of the athetoid type.

Himwich has shown that the highest rate of metabolism occurs in the gray cells of the cortex. In this case the patient was deprived of oxygen and consequent damage might be expected to occur in that location. It also is a fact that barbiturates slow up cellular metabolism in the brain, and consequently whenever a patient receives nitrous oxide there should always be a careful inquiry of how much barbiturates she has received.

DR. ALEXANDER H. ROSENTHAL.—The Committee on Analysis of Maternal Deaths in Brooklyn, during the years 1937, 1938, and 1939, assigned the primary cause of death in 13 patients to the anesthetic employed, in a series of 387 consecutive maternal deaths from all causes. The record compares unfavorably with the report of maternal mortality in New York City for the years 1930 to 1933 in which anesthesia was considered the direct cause of death in 20 cases out of a total of 2,041 deaths. The frequency of death from anesthesia in Brooklyn was thus more than three times as high.

A review of the 13 deaths showed that five were in patients delivered by cesarean section, four by forceps, three spontaneously, while one patient was undelivered.

Three patients received only spinal anesthesia. In one of the deaths, anoxia, of a type Dr. Turino has described tonight, may have occurred. In 5 patients death was due to vomiting and aspiration, 2 proved at autopsy by the presence of food particles in the tracheobronchial tree. In two cases general anesthesia was used in the presence of toxemia.

The dangers in the use of anesthesia in obstetrics should be well known, and certain facts self-evident.

1. The administration of a general anesthetic should be reduced to a minimum. In spontaneous deliveries, the perineal stage of labor and the episiotomy with its repair can be more safely done under local anesthesia, which especially is indicated in toxemia, cardiac disease, tuberculosis, and upper respiratory infections.
2. The stomach should be free of food before the induction of general anesthesia.
3. The risk of general anesthesia is increased in the presence of toxemia.
4. Spinal anesthesia should not be used by the occasional obstetric operator. It carries particular dangers for the pregnant woman.

DR. FREDERICK C. WILCOX, JR.—George Savage of Great Britain, in 1887, reported a case like this one in the *British Medical Journal*. His patient was an alcoholic, a young woman, who became frankly demented after nitrous oxide anesthesia, and evidently she did not recover. Courville, of Los Angeles, and Batten, of Battle Creek, in a recent article in *Anesthesiology* reported 10 cases, 5 of which had previously been reported. The end-results in all these cases ranged from complete recovery down through impairment of memory and emotional instability, to death.

Four of these reported cases had definite secondary anemia, so that with the anoxia produced by the nitrous oxide there undoubtedly was some anoxia due to anemia. It is of interest to note that 6 of the patients were obstetric and gynecologic cases. The explanation for so many of these cases in obstetrics possibly may be that obstetric patients at term, as a rule, have a higher basal metabolic rate than usual, sometimes being 20 per cent above normal, and need a greater percentage of oxygen than under ordinary circumstances.

Nitrous oxide, as has been stated, depends partially upon anoxia for its anesthetic action. It has hazards, except under most ideal conditions, and I should like to state the conditions which I think are ideal for its use: "(1) The basal metabolic rate should be normal. (2) The blood count and hemoglobin should be approximately normal. (3) There should be no history of chronic alcoholism. (4) Adequate premedication should be given the patient. (5) The patient should be of the white race."

DR CHARLES A. GORDON.—It is absolutely impossible to get anesthesia with nitrous oxide in any concentration that does not approach 100 per cent. Otherwise we get analgesia but not anesthesia. The anesthetist, when he or she finds that the operator is dissatisfied, is likely to crowd the percentage of gas so that it approaches very undesirable levels.

From what we know about nitrous oxide, and the autopsy findings in this case, I believe that undue concentration was used. No one should use it unless he pays attention to the anesthetist so as to make sure that the concentration is as the operator thinks it should be; otherwise it is dangerous. Nitrous oxide has a great many advantages and when combined with local anesthesia and proper infiltration, it is safe and satisfactory.

JELLY CONTRACEPTIVES*

A Three-Year Investigation

Irving F. Stein, M.D., and Melvin R. Cohen, M.D., Chicago, Ill.
Assisted by Rita Nielsen, R.N.
(From the Michael Reese Hospital and Northwestern University Medical School)

SOME ten years ago, one of us (Stein) concluded a three-year study using jelly alone for contraception in a series of 146 fertile women. These patients, observed from six months to two years, using a 2 per cent lactic acid jelly with chinosol, were afforded a high degree of protection. In fact, during the course of the active clinic, no pregnancies were discovered and only after the clinic was disbanded and patients spread over the five regular gynecologic clinics of Mandel Clinic, did a number of pregnancies occur. Records of some of these women who are still registered at Mandel Clinic show that they have used jelly continuously and effectively up to the present time.

In the interim, we have followed this method of contraception to some extent in our private practice with a degree of success sufficient to warrant another inquiry as to its efficacy, using modern and improved preparations which are now commercially available. We have felt that there is a definite need for a simple, safe and inexpensive single method of birth control, one which will prove to be acceptable to both husband and wife, and be within easy reach when needed. Such a method must also be one not likely to lessen natural desires and responses; it must be effective as a contraceptive and at the same time harmless to the patient. Consequently, when requested by the National Committee on Maternal Health to investigate "jelly alone" again, we reorganized a special Birth Control Clinic at the Mandel Clinic of the Michael Reese Hospital.

It was decided that this clinic should accept *medical referrals only*, no voluntary requests for birth control being granted. Patients were referred from the gynecologic, postnatal, psychiatric, medical (especially cardiac and tuberculosis), and other departments of Mandel Clinic. Careful records were kept and a history of previous pregnancy and labor, abortions, and previous birth control experience were particularly noted. Reasons for acceptance or refusal of patients for jelly contraception were recorded, and the kind of jelly and applicator issued was stated (Figs. 1 and 2). Upon follow-up visits, questions were asked and answers recorded as to whether instructions were followed; discontinuance of the method or omission; whether or not the jelly was satisfactory to husband and wife; objections to the method; whether pregnancy occurred while the method was in use. In the event of the latter, further inquiry was made into reasons for the same.

*Presented at a meeting of the Chicago Gynecological Society, December 20, 1940.

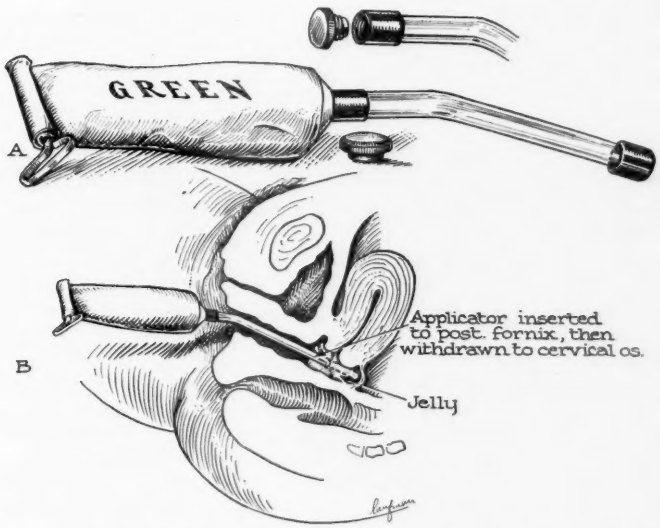

Fig. 1.—"Green" jelly. Key dose control. Attached nozzle. *Formula:* Lactic acid, 2.0 per cent; oxyquinoline sulphate, 0.05 per cent; durekol base (made of especially blended carbohydrate gums). pH 2.9.

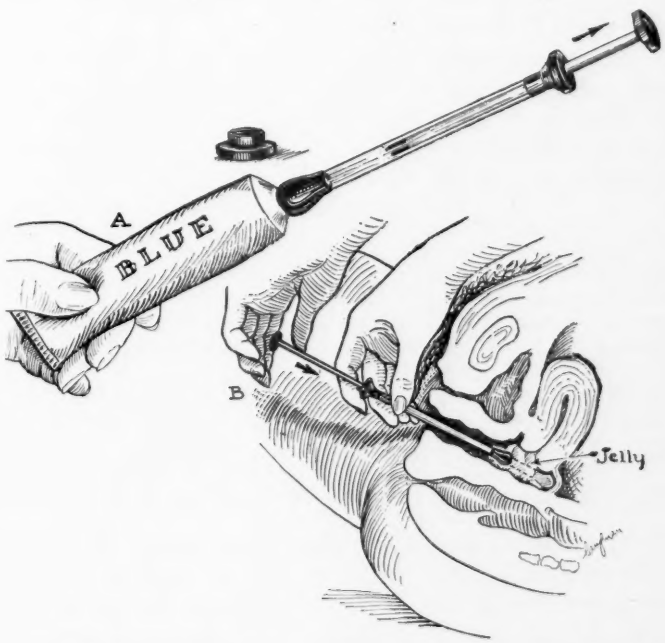

Fig. 2.—"Blue" jelly. Measured dose applicator. *Formula:* Glycerin, 10.0 per cent; vegetable gum, 5.0 per cent; boric acid, 3.0 per cent; ricinoleic acid, 0.75 per cent; propyl ester of para-hydroxy-benzoic acid, 0.05 per cent; oxyquinoline sulphate, 0.025 per cent; perfume, 0.05 per cent; water to 100.0 per cent. The pH is 4.5.

RESULTS

Altogether, 310 patients were registered in the special Birth Control Clinic. Two-thirds reported that they had previously used various and often multiple contraceptive methods more or less unsuccessfully. Only 79 women reported that they had previously used no means of contraception, and it is more than likely that a number of these had practiced coitus interruptus, the one single method most frequently employed by those who admitted previous birth control. The next in order of frequency were the postcoital douche and the condom, reported in about equal numbers. The douche proved to be the most disastrous, yielding a high percentage of undesired pregnancies, practically paralleling those who used no previous birth control. The condom gave the highest degree of pre-clinic protection. The use of a diaphragm and jelly combination was reported by a relatively small group (22 women) with failures in more than half the cases. However, many of these failures might be attributed to the fact that instruction in the use of the diaphragm was inadequate, some having purchased the materials in drug stores or obtained them from physicians untrained in birth control procedures. A small group used jellies for varying periods up to eight years. A few of these were holdovers from our former clinic. Fully one-fourth of the group reported having tried a variety of methods, single and combined, but generally with unsatisfactory results.

To evaluate the effectiveness of jelly alone as a contraceptive agent, the method of Pearl as modified by Stix and Notestein was adopted. Pregnancy rates were computed for patients before using the clinic prescription and compared with those obtained after using the jelly method. *The pregnancy rate is expressed in the following equation: The number of pregnancies divided by the exposures in years to the risk of pregnancy, multiplied by 100.*

The effectiveness of the method is expressed as percentage reduction in fertility. A summary of the effectiveness of jelly alone in our three-year study gave a total reduction in fertility of 87.1 per cent.

Failures were considered from the standpoint of: (1) failure of the jelly-alone method as instructed; (2) failure to use the method, or irregular use; (3) failures after discontinuing the method, including planned pregnancies; (4) failures in women who used other methods than the one prescribed.

1. There were 20 patients in the entire series who presumably became pregnant while using the jelly alone as instructed. These must be construed as true failures, and in terms of percentage, constitute 8.6 per cent of patients who remained in the clinic from three months to three years.

2. There were 18 women who admitted inconstant use of jelly and omission of the preparation at the time of conception. These obviously cannot be termed as jelly failures.

3. Three women discontinued the method in order to become pregnant (planned pregnancies).

4. Two pregnancies occurred in women who were relying upon condom protection instead of the prescribed jelly. In addition, a miscellaneous group included one who was judged incompetent to follow even the simple instructions of the jelly technique.

There was a total of 47 women who became pregnant, including the planned pregnancies, in the entire group. Seventeen of these delivered at term and 8 were pregnant at the termination of the clinic. The wastage may be expressed by 2 stillbirths, 9 spontaneous and 5 induced abortions. In addition, there were 6 whose terminations were unknown.

SUMMARY

1. It has been shown by Stix that birth control measures are not equally effective in reducing the risk of pregnancy in the various social

classes. She concluded that the condom is only 65 per cent effective in relief recipients in comparison with 88 per cent effectiveness in white-collar workers. The clientele represented in our study was drawn essentially from families on relief.

2. Of the 310 patients who registered in our Birth Control Clinic at Mandel Clinic, 231 remained active for a period ranging from three months to three years. They made a total of 816 clinic visits. Most of the patients who accepted the method and cooperated with us were contented with it.

3. An analysis of preclinic experience revealed that two-thirds of the patients had previously used various birth control methods, both single and combined, with unsatisfactory results.

4. A total of 47 pregnancies occurred in the active clinic group, but when these histories were analyzed, only 20 could be charged against the jelly-alone method.

5. The results of this study confirm our opinion regarding the value of the jelly-alone method which was based upon our previous experience with this method a decade ago.

6. The effectiveness of jelly alone as a contraceptive is shown by the 87.1 per cent reduction in fertility. This compares most favorably with the results of the diaphragm and jelly method which Stix has shown was only 76 per cent effective in relief recipients, a clientele similar to ours.

7. Acceptability of the method is proved by the fact that while 37 per cent of the total group, or 50 per cent of the group active in the clinic for some time, used the method, a very small number had any real objection to or complaint against the method. Because of the low acceptability of any single method of birth control, multiple techniques should be available in birth control clinics.

8. In our opinion, *it is the jelly and not the diaphragm that is the potent factor in the diaphragm and jelly technique of contraception.*

CONCLUSIONS

Early in this discussion we have defined what we consider the basic requirements for a simple and safe contraceptive, namely: that it must prove acceptable to both husband and wife; it must always be within easy reach; it should not lessen natural desires and responses; it must be effective and at the same time harmless. The jelly-alone method in our experience measures up to these standards.

In conclusion, we believe that clinics should not limit their procedure to a single method, but should adopt a more flexible policy of utilizing the various accredited techniques, fitting the contraceptive to the needs of the individual patients. Whenever the patient is dissatisfied with the method prescribed, a different one should be substituted, thereby not only suiting the contraceptive to the patient, but also increasing her confidence in the method. So far as the jelly-alone method is concerned, many patients who had been judged as below average in intelligence and who were supposedly unable to follow directions, proved capable of

utilizing the technique with complete success for long periods of time. Of this group, a few were so well satisfied with the method that they refused sterilization which had previously been proposed.

Jelly alone should be included in the list of approved contraceptive techniques.

DISCUSSION

DR. FRED L. ADAIR.—We have had no experience whatever in our clinic with the use of jelly alone. We have used various other methods which seemed to be approved and most generally used in other clinics. Our situation is somewhat different from Dr. Stein's and other so-called birth control clinics, because we run our contraceptive clinic simply as a part of the Maternity Guidance Clinic. It is open only to patients who come to the clinic for other purposes. Second, most of the patients who receive contraceptive advice are those who require it for medical complications. We have had no experience with methods that are not considered reliable, as we do not feel justified in experimenting with patients to whom pregnancy would be a hazard.

The great difficulty with all contraceptives from a sociologic point of view is that the methods do not reach the people who need them most. It is all right to find a method which is harmless, which is used by a little over one-third of the people who apply to the clinic, and which is effective when properly used by patients in 87 per cent, which still leaves 13 per cent of failures. There are many people who do not continue to use it even though they seek advice at the clinic. Also, there is a great mass of people who from the standpoint of environment, heredity, and other conditions should have this sort of advice but who never get into a birth control clinic. So from the standpoint of sociologic problems involved, it has always seemed to me that we are not reaching the patients who need to be reached the most. However, that is no reason for not employing these methods as indicated in individual cases. Two years ago we presented before this Society a procedure which is relatively harmless, much more effective, and one in which the patient does not need to use her intelligence, the so-called post-partum sterilization. This procedure was not received too kindly in this Society, but we have continued to employ it nevertheless. From other clinics we have received favorable reports. One of our former residents now located in Puerto Rico, where the control of conception is badly needed, has had a considerable series of cases in which post-partum sterilization has proved both satisfactory and safe. In those patients who should never become pregnant again, I would call attention to this post-partum sterilization which is safe and does not menace the patient in the properly selected cases when properly performed.

DR. H. O. MARYAN.—About three years ago I helped develop a contraceptive jelly, and made a study of the patients along clinical and laboratory lines. I should like to report some observations made in 30 cases.

We first took into consideration the psychic reaction; that is, the presence or absence of local irritation. I do not know of any article in the literature that takes up this phase. I think that this is very important because of the toxicity of the various contraceptive jellies. Another phase we took into consideration was the healing value in irritations of the vagina and cervix, and also the spermatocidal value.

One of the most usual complaints of the patients was that the jelly was "messy" and that it would run out during the night. However, many husbands were not aware of the fact that their wives were using jelly. Women like it because it is cleaner, and also because it gives a better vaginal odor, as well as the fact that it aids in healing areas where biopsies were taken. We made biopsies from the vagina in five cases. The pharmaceutical house also made cervical and vaginal biopsies on monkeys before the jelly was used in women. We found there was no cervical or vaginal irritation after the patient had used the jelly for several months. The patients were instructed to use the jelly every night. These specimens were checked

by several leading pathologists in the country. Irritation is one of the most important things we have to contend with in jelly put out by a company that is not controlled.

We found with the contraceptive jelly that sperms are killed in one minute. With contraceptives other than jelly, we found that they will live for two to three hours. All the semen we studied was checked for fertility.

DR. CHARLES E. GALLOWAY.—Dr. Stein has given us an honest paper and has acknowledged that 47 of his patients became pregnant.

I want to bring out the point that we as physicians should tell these patients who want to know if they can have intercourse and still not become pregnant, that there is no method of contraception that will not fail. Any one of them will have from 8 to 13 per cent of failures. I tell my patients that the rubber condom, contraceptive jelly, and hot water douche with each intercourse are fairly effective. If they want to be a little more secure then, in addition to the three things mentioned above, they can use a diaphragm. Then they often tell me that one or the other objects to the condom or some of the other things mentioned. I tell them if they cannot use the condom, they either do not need intercourse or they are very weak sexually. In other words, I think we as physicians should treat this subject rationally, and not as public appeasers.

DR. COHEN (closing).—In answer to Dr. Adair, we limited our 310 patients to those who had medical indications only. We had hoped to extend the indications to those who sought advice for economic reasons or for child spacing, but our hospital authorities did not sanction such a policy. We obtained 87 per cent reduction in fertility which compares favorably with the use of the diaphragm-jelly method in a similar clientele.

In reply to Dr. Maryan, our jelly preparations showed no toxic effects and produced no local irritation. Two patients who complained of burning were found to have trichomonas vaginitis. The spermatocidal value of the jelly preparations was well proved before clinical use.

In reference to Dr. Galloway, who commented about our frankness in reporting 47 failures, I question whether all of the patients were telling the truth. When I was first asked to handle the birth control clinic with Dr. Stein, I was very skeptical about the value of jelly alone. I thought the method could not be effective but was gratified to find that so many patients were adequately protected.

Simon, Clement: Bismuth Cervico-Vaginitis, Presse méd. **48**: 351, 1940.

Bismuth cervicovaginitis, like bismuth stomatitis, may occur in various clinical patterns. Sometimes the lesion consists of punctate, stainlike patches, blackish blue in color. In other cases the lesion may be erosive, ulcerative or even occur as a slough. The more extensive lesions may appear as very adherent grayish, pseudomembranes covering the portio of the cervix and extending ringlike about the mucosal walls of the upper vagina. The underlying tissue becomes edematous, ulcerated and even gangrenous, and may give rise to repulsive leucorrhea or even serious vaginal hemorrhage, as in the first case reported by the author in 1933.

This complication of bismuth treatment is asymptomatic except in those cases presenting a greater degree of tissue involvement.

The pathogenesis of bismuth cervicovaginitis is the same as that of bismuth stomatitis, minute deposits of sulfurated bismuth obstructing the smaller capillaries and producing erosions or even slough by infarction.

The author contends that the condition is not uncommon and that more cases will be found if those female patients receiving bismuth therapy be submitted to frequent speculum examinations. His patients are examined twice each week.

CLAIR E. FOLSOME.

OBSERVATIONS ON THE OCCURRENCE OF CLOSTRIDIUM WELCHII IN THE VAGINA OF PREGNANT WOMEN

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CONSTANTINO P. MANAHAN, M.D., BALTIMORE, MD.,
WITH THE TECHNICAL ASSISTANCE OF EDWIN H. STEWART
(From the Department of Obstetrics, the Johns Hopkins University and Hospital)

CL. WELCHII, also commonly known as *Bacillus aerogenes capsulatus* and the gas bacillus, is a rather short, nonmotile, gram-positive rod, growing under fairly strict anaerobic conditions. It forms capsules in the animal body and under certain conditions readily sporulates. A so-called stormy fermentation of milk, with formation of clot, acid, and gas, is characteristic. Classification into four types, A, B, C, and D, is recognized, but only Type A is met with in the human body. Hemotoxin and myotoxin are produced, thus accounting for certain characteristic clinical observations. The response to sulfanilamide of clinical infections by this organism has been described.[1-3]

The gas bacillus is found in soil, water, milk, dust, sewage, and the intestinal canal of man and animals. Its occurrence normally in the human vagina has aroused much debate and discussion.

Stander[4] denies that the organism is an inhabitant of the normal vagina, while Curtis[5] believes that it is only rarely present in normal ante-partum or post-partum cases. Wrigley,[6] in a study of 150 cases during labor or the post-partum period, was not able to culture the gas bacillus from the cervical canal or from the lochia, though he did find a positive culture in 13 of 69 cases in which the pregnancy, labor, or puerperium was abnormal.

Contrary to the above views, others have demonstrated that the gas bacillus may be present with surprising frequency in the normal vagina. Schottmüller[7] first brought attention to this fact in 1910. Falls[8] cultured the vagina of 270 prenatal patients and found that *Cl. welchii* was present in 5.6 per cent of the cases. Likewise, Bysshe[9] was able to demonstrate 4.5 per cent positive cultures from the vaginas of 547 ante-partum and post-partum patients. Unfortunately, in both of these studies, certain bacteriologic data necessary for absolute confirmation or identification of the gas bacillus are lacking. Also, the virulence of the strains isolated was not determined.

Our attention was attracted to this problem recently by a case of *Cl. welchii* endometritis occurring after therapeutic abortion, details of which have been published elsewhere.[2] In this patient the only likely source of contamination with the organism was the vagina. This fact, together with the present state of disagreement concerning the absence or presence of the gas bacillus in the vagina of the normal pregnant female, prompted us to investigate the problem.

In this paper are recorded: (1) Observations on the vaginal culture for *Cl. welchii* in 219 consecutive patients from the Prenatal Clinic of the Johns Hopkins Hospital; (2) a complete bacteriologic study of

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the strains isolated, with data on the virulence of each strain; and (3) an analysis of labor and the post-partum period in each patient with a positive culture for the gas bacillus.

METHOD OF STUDY

The data presented in this study are based upon 132 colored patients and 87 white patients attending the Prenatal Clinic of the Johns Hopkins Hospital. A single vaginal culture was taken, with subsequent culture being taken in those instances where a positive culture for *Cl. welchii* had been obtained.

The vaginal culture was obtained by separating the labia and inserting a swab deep in the posterior vault, taking care to avoid contamination. In certain instances where absence of contamination by the labia could not be assured, or during the last month of pregnancy, a sterile speculum was first inserted. During labor and in the post-partum period, insertion of the sterile speculum was preceded by preparation of the perineum with Scott's solution.

The swabs were then immediately taken to the laboratory and twirled vigorously in a tube of cooked meat medium, following which the latter was sealed with sterile vaseline. After incubation at 37.5° C., for twenty to twenty-four hours, the vaseline seal was broken and a defibrinated rabbit's blood agar plate was streaked with a loopful from those tubes in which either gas production was observed, or smear revealed the presence of gram-positive bacilli. These plates were incubated anaerobically for twenty-four hours at 37.5° C. At the end of this period the plates were inspected for colonies of *Cl. welchii*, which were recognized by the characteristics of the colony and the production of a beta type of hemolysis. The latter was often associated with a double zone appearance of hemolysis; that is, an area of complete hemolysis immediately about the colony, with a ring of incomplete hemolysis, or deeper line about the area of complete hemolysis. The individual colony was then transferred to cooked meat under vaseline. With a pure culture thus obtained, the various bacteriologic reactions were studied.

Motility.—Observations of motility were made on hanging drop preparations of an eight- to sixteen-hour cooked meat media under vaseline.

Litmus Milk.—Inoculation of litmus milk media under vaseline was carried out with observation of the so-called stormy fermentation of milk.

Gas Production.—Estimations of the relative production of gas in cooked meat media under vaseline were made on twenty- to twenty-four-hour cultures.

Hemolysis.—Deep defibrinated rabbit's blood agar plates were inoculated with a properly diluted culture of the organism and observations made upon the type of hemolysis produced after twenty-four hours of incubation at 37.5° C.

Soluble Hemolysin.—The presence of a soluble hemolysin for rabbit red cells was demonstrated by incubating in a 37.5° C. water bath for one hour a mixture consisting of 0.5 c.c. of 5 per cent washed rabbit cells and 0.5 c.c. of a twenty-hour cooked meat culture of the organism.

Virulence Test.—Five-tenths cubic centimeter of a twenty-hour cooked meat culture of the organism was injected intramuscularly into the thigh of a 250 Gm. guinea pig. In the event of death, which usually occurred sixteen to forty hours after injection, examination and culture of the leg lesion and cultures of the blood stream for the Welch bacillus were carried out.

RESULTS AND DISCUSSION

The clinical results obtained are summarized in Tables I and II, with the bacteriologic characteristics of each strain isolated being detailed in Table III.

In the series of 219 patients, 19, or 8.7 per cent, yielded a postive vaginal culture for *Cl. welchii*. As outlined in Table III, each of the 19 strains of the Welch bacillus was a gram-positive rod, nonmotile, growing only anaerobically and producing stormy fermentation of milk. Gas production in cooked meat was moderate to marked, and

in all instances a strong hemolysin for rabbit cells was demonstrated. Beta hemolysis in deep rabbit's blood agar plate was invariably present. In some instances, a surrounding zone of incomplete hemolysis was present; in others, a ring of deeper hue was seen. The virulence test, as determined by death of a guinea pig, with positive blood culture for *Cl. welchii,* was positive in 9 of the 19 strains, or approximately one-half.

The data in Table I demonstrate that there was no essential difference between the colored and white group, figures of 9.1 per cent and 8.1 per cent, respectively, being obtained. One patient of the 19 failed to return to the clinic after the first visit, hence part of the data analyzed depend on a total of 18 patients with positive vaginal cultures.

TABLE I. PREGNANT PATIENTS HAVING A POSITIVE VAGINAL CULTURE FOR CL. WELCHII DURING THE ANTENATAL PERIOD

	NO. OF PATIENTS CULTURED	NO. OF PATIENTS WITH POSITIVE CULTURES
Colored	132	12—9.1%
White	87	7—8.1%
Total	219	19—8.7%

In no single instance was the gas bacillus a permanent inhabitant of the vagina. Even in Case 15, in which the vaginal culture was positive during the second and third trimester and labor, the gas bacillus was not present during the post-partum period. It is of interest, however, to point out that in each instance in which the organism was found to be more or less persistent in the vagina, such as Cases 1, 5, 15, and 17, the virulence test for the particular strain was always positive. In one instance this was due to acute mastitis. In a fifth case (Case 6), the febrile puerperium was definitely ascribable to an intrauterine infection with an anaerobic, nonhemolytic streptococcus, the temperature being elevated from the third to the fifth day, inclusive, and reaching as high as 103.2° F. Both vaginal and intrauterine cultures were negative for *Cl. welchii.*

In addition to the 19 strains of *Cl. welchii* presented above there were also found two anaerobic gram-positive rods which were motile. These were not included in this group, since there are said to be several species of motile anaerobic bacilli[10] apart from *Cl. welchii* which produce stormy fermentation in milk.

Approximately one-third of the patients with a positive vaginal culture, or more exactly 31.6 per cent, were primiparas. This ratio is essentially similar to the ratio of 28 per cent in the 200 patients with negative vaginal cultures. The fact that cultures from so many primiparas were positive is perhaps surprising, since it has been commonly assumed, as first pointed out by Falls,[8] that patients with relaxed perineal outlets were more likely to harbor the gas bacillus, since this organism is invariably found in the human stool.

Puerperal infection was no more frequent in the group with positive vaginal culture than in women with negative culture. The present study would suggest, moreover, that the presence of the Welch bacillus

TABLE II. DATA ON PREGNANT PATIENTS IN WHICH A POSITIVE VAGINAL CULTURE FOR CL. WELCHII WAS OBTAINED, THE STUDY INCLUDING 132 COLORED PATIENTS AND 87 WHITE PATIENTS

CASE	RACE	PARITY	GRAVID	CULTURE OF VAGINA FOR CL. WELCHII								POST-PARTUM PERIOD				PREMATURE RUPTURE MEMBRANES
				ANTENATAL PERIOD TRIMESTER				POST-PARTUM PERIOD DAY				TEMPERATURE	TYPE OF DELIVERY	HOURS OF LABOR		
				1ST	2ND	3RD	LABOR	3RD	4TH	5TH	6TH			HR.	MIN.	
1	C.	5	6			+	−		+			Afebrile	Spont.	8	20	24 hr.
2	C.	0	0		+		−	−				Febrile* 1 day	Spont.	11	51	−
3‡	C.	1	1		+											
4	C.	8	11	+	−		−	−				Febrile 1 day	Spont.	3	47	−
5	C.	4	5			+	−			+		Afebrile	Spont.	10	25	−
6	C.	4	4			+	−			−		Febrile†	Spont.	1	30	7 hr.
7	C.	1	1			+	−	−				Afebrile	Spont.	16	18	29 hr.
8	C.	3	3		+		−	−				Afebrile	Spont.	3	13	−
9	C.	8	8		+		−			−		Afebrile	Spont.	6	32	−
10	C.	1	1		+		−		−			Afebrile	Spont.	26	11	−
11	C.	4	4	+	−		−		−			Afebrile	Spont.	5	4	−
12	C.	0	0	+	−		−			−		Afebrile	Spont.	3	26	
13	W.	10	10			+	−	−				Febrile 1 day	Spont.	8	16	8 hr.
14	W.	0	0		+	−	−				−	Febrile 1 day	Low forc.	8	43	−
15	W.	1	1		+	+	−		−			Afebrile	Low forc.	13	14	−
16	W.	0	0		+	−	−		−			Afebrile	Low forc.	6	22	−
17	W.	0	0		+	+	−					Afebrile	Low forc.	8	15	−
18	W.	1	2	+	−	−	−				−	Afebrile	Spont.	32	34	8 hr.
19	W.	0	0		+	−	−		−			Afebrile	Low forc.	3	26	3 hr.

*International nomenclature, T. 100.4° or higher.

†Febrile third to fifth day post partum, due to intrauterine infection with anaerobic nonhemolytic streptococci. Intrauterine culture negative for *Cl. welchii*.

‡Patient failed to return after first visit to clinic.

TABLE III. BACTERIOLOGIC DATA ON STRAINS OF CL. WELCHII ISOLATED FROM THE VAGINAL CULTURES OF CASES DETAILED IN TABLE I

CASE	GROWTH ON BLOOD AGAR		MOTILITY	STORMY FERMENTATION OF MILK	GAS PRODUCTION IN COOKED MEAT UNDER VASELINE	HEMOLYSIS ON BLOOD AGAR POUR PLATE†	SOLUBLE HEMOLYSIN	VIRULENCE TEST (GUINEA PIG)*
	AEROBIC	ANAEROBIC						
1	–	4+	–	4+	2+	Beta type	4+	+
2	–	4+	–	4+	3+	Beta type	4+	–
3	–	4+	–	4+	2+	Beta type	4+	–
4	–	4+	–	4+	2+	Beta type	4+	+
5	–	4+	–	4+	4+	Beta type	4+	+
6	–	4+	–	4+	4+	Beta type	4+	–
7	–	4+	–	4+	4+	Beta type	4+	–
8	–	4+	–	4+	3+	Beta type	4+	–
9	–	4+	–	4+	4+	Beta type	3+	+
10	–	4+	–	4+		Beta type	4+	–
11	–	4+	–	4+		Beta type	4+	+
12	–	4+	–	4+		Beta type	4+	+
13	–	4+	–	4+	4+	Beta type	4+	–
14	–	4+	–	4+	2+	Beta type	4+	–
15	–	4+	–	4+	4+	Beta type	4+	+
16	–	4+	–	4+		Beta type	3+	–
17	–	4+	–	4+	4+	Beta type	4+	+
18	–	4+	–	4+	4+	Beta type	4+	–
19	–	4+	–	4+	4+	Beta type	4+	+

*0.5 c.c. of twenty-hour cooked meat culture injected intramuscularly into thigh of 250 Gm. guinea pig. Death in sixteen to forty hours, with recovery of organism in local lesion and from the blood stream.

†Double zone hemolysis in all cases except cases 6 and 13.

in the vagina, even during labor or the post-partum period, as in Cases 1, 5, and 15, does not necessarily imply that imminent danger of intrauterine infection is to be feared, since all three of these patients were afebrile. It should also be added that these cases were uncomplicated obstetrically. When, however, traumatized or devitalized tissue is present and the organisms are carried from the vagina into the uterus, then conditions are set up which cause the gas bacillus to propagate rapidly and produce an endometritis.[2] This concept is by no means original with us, since these factors have been stressed by practically every author writing on the subject of *Cl. welchii* postabortal or puerperal infection.

In 18 patients in this series, 4 (22.2 per cent) had a one-day fever.

SUMMARY AND CONCLUSIONS

1. In a study of 219 normal prenatal patients, 8.7 per cent were found to have *Cl. welchii* by vaginal culture; 9.1 per cent of the colored women and 8.1 per cent of the white women had positive cultures.

2. Of the 19 strains of *Cl. welchii* isolated, 9 were "guinea pig" virulent.

3. *Cl. welchii* was not a permanent inhabitant of the vagina in any of the patients.

4. The number of primiparas yielding positive vaginal cultures would suggest that perineal relaxation is not the main factor in contamination of the vagina by *Cl. welchii* from the feces.

5. Puerperal infection was no more frequent in the group with positive vaginal culture than in women with negative vaginal culture.

6. Isolation of the gas bacillus from the vagina in three cases, either during labor or in the puerperium, would demonstrate that the recovery of this organism from the vagina does not necessarily imply infection with the Welch bacillus, since all three patients remained afebrile and presented no evidence of puerperal infection.

7. The above results would indicate that *Cl. welchii* may be found normally in the vagina of the adult pregnant female, but that it is not necessarily a permanent inhabitant.

8. Recovery of the gas bacillus from the normal vagina is not necessarily of serious import, but in the presence of traumatized or devitalized tissue, serious infection with the gas bacillus may result.

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CLINICAL EXPERIMENTS WITH DIETHYLSTILBESTROL*

I. Estrogen Withdrawal Bleeding in Primary and Postmenopausal Amenorrheic Women

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Zuckerman[5] has introduced the theory of a uterine threshold to estrogen into the picture of the menstrual mechanism of the rhesus monkey. He writes: "The concept of an oestrone threshold of the uterus in primates is open to at least three interpretations. It might mean the least amount of hormone necessary to produce, in the shortest possible time, definite signs of endometrial growth in a spayed monkey. It might mean the least amount of hormone, given over a stated number of days, that is needed to influence the endometrium sufficiently for the cessation of injections to be succeeded by uterine bleeding. Or it might mean the smallest dose which, given daily for an indefinite period, will maintain the endometrium without uterine bleeding occurring." Zuckerman's experiments are concerned primarily with the second interpretation. In effect, bleeding occurs when the uterine threshold rises above the amount of estrin present, or when the amount of estrin present falls

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below the uterine threshold. In other words, the relative levels of these two factors with respect to each other seem to be the state which, if it could be measured, determines the presence or absence of uterine bleeding.

Zuckerman[5, 6] has produced uterine bleeding in the ovariectomized monkey in two ways. By varying the manner in which estrone is administered, *cyclical* phases of uterine bleeding were induced, reflecting on the one hand the fluctuation of the estrin level and on the other the fluctuation of the uterine threshold.

Fluctuation of Estrin Level in the Monkey.—(Zuckerman.[6]) In order to simulate what is generally believed to be the normal production of estrin by the ovary, it was necessary to supply estrogen in increasing and suddenly decreasing amounts of the hormone; when the latter is given in increasing amounts in a fourteen-day period,

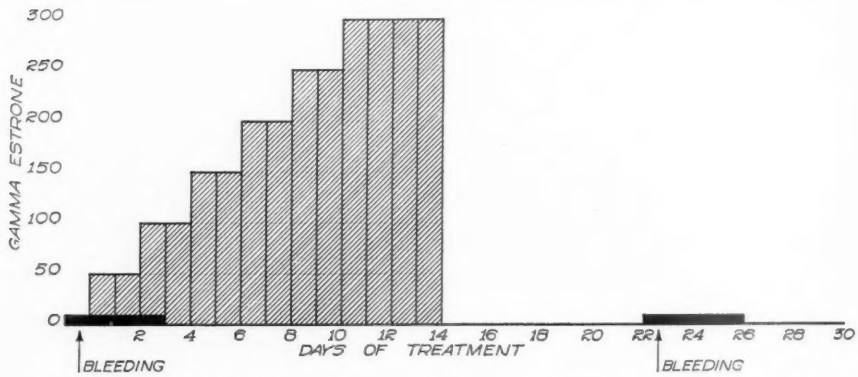

Fig. 1.—Threshold cycle in monkey produced with estrone. (Zuckerman, 1937.)

beginning with the onset of menstruation, the treatment is comparable to the time for growth and rupture of the graafian follicle. Estrin produces its positive morphologic effects in the endometrium during the first half of the normal cycle in the rhesus monkey as well as in the human female. To simulate the sudden fall of estrin level that occurs following the rupture of the Graafian follicle, the daily injections of the hormone were stopped after the fourteenth day. An optimum amount (experimentally) of estrone required to influence the endometrium of a monkey in fourteen days so that cessation of injections would be followed by uterine bleeding was found to be 2.7 mg., administered as shown in Fig. 1.

Bleeding occurred regularly on the twenty-second or twenty-third day of the "artificial" cycle or eight to nine days after cessation of injections, indicating that the cessation of therapy on the fourteenth day was followed by a fall in the level of estrin below the uterine threshold on about the twenty-second or twenty-third day. The uterine bleeding thus produced was a reflection of a fluctuating (falling) estrin level. In order to lengthen the artificial cycle from twenty-two to twenty-eight days, a daily subthreshold dose of estrogen was started on the fifteenth day which was sufficiently small to allow the estrin to fall more gradually to a level below the uterine threshold and sufficiently great to prevent the uterine threshold, if fluctuating, from rising above the estrin level before the twenty-eighth day. The daily dose of estrone necessary for this purpose in the monkey was found by Zuckerman to be 10 to 15 gamma (Fig. 2).

As soon as bleeding began the animal was started on a new cycle. The production of an artificial cycle constitutes the nearest approach to the way in which the ovary produces its effect during an anovular cycle that has yet been recorded. The

ovulatory cycle in which progestin takes part has also been simulated and produced artificially (Zuckerman[7]); this particular issue is not, however, relevant to the clinical experiment under discussion.

Fluctuation of Uterine Threshold in the Monkey.—The fluctuating uterine threshold has been demonstrated by Zuckerman[5] in an ovariectomized monkey which was injected daily for 365 days with the same amount of estrone (10 gamma per day). In spite of the repeated injections, eight separate phases of bleeding occurred during the experiment but at intervals varying from five to seven weeks. In view of the fact that uterine bleeding will not occur in spayed monkeys under continuous injection with an amount of hormone that is well above threshold value (100 gamma per day), the successive phases of bleeding observed in this monkey must be interpreted as reflections of successive falls in the degree of estrogenic stimulation experienced by the animal or successive rises of the uterine threshold. Since the monkey was being continuously injected with the same amount of hormone daily, it follows that rhythmical changes of a kind that decreased the effectivity of the hormone occurred within the animal itself. The possibility that the adrenals and the pituitary are in some way concerned is being investigated.

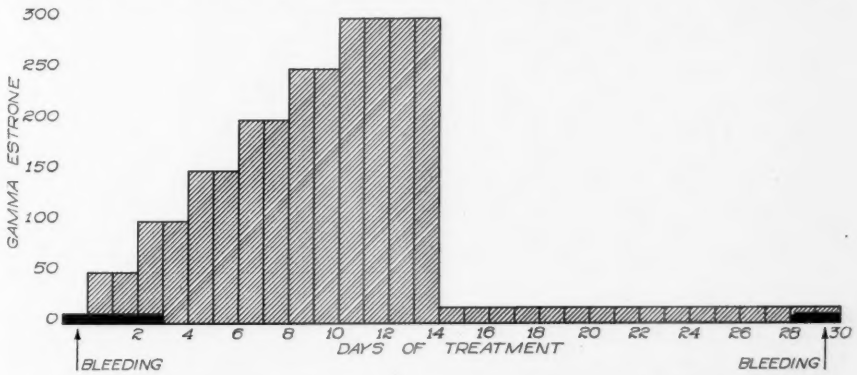

Fig. 2.—Threshold cycle in monkey produced with estrone. Length of cycle prolonged from 22 to 28 days with daily subthreshold dose of estrone from fifteenth day forward. (Zuckerman, 1937.)

ARTIFICIAL CYCLES IN THE HUMAN BEING

I have used diethylstilbestrol in the human being to induce cyclical estrogen withdrawal bleeding. Wenner and Joël[4] and Wenner[3] report that a minimum total dose of 25 mg. of diethylstilbestrol orally is required to produce what appears to be normal endometrial growth, while a dose of 60 mg. or more may produce endometrial hyperplasia. The availability of 1 and 5 mg. tablets of diethylstilbestrol resulted in the adoption of the following plan for the production of an artificial estrogenic cycle in the human subject: 1 mg. per day for seven days followed by 5 mg. per day for seven days. Thus one course of therapy would amount to a total dose of 42 mg.

The treatment of 4 patients with primary amenorrhea in this manner was usually followed by uterine bleeding after a latent interval of five or six days (Table I). Prolongation of the latent interval was effected in 3 artificial cycles by giving a subthreshold dose of 0.1 or 0.3 mg. of diethylstilbestrol daily from the fifteenth day onward. The pH of the vaginal mucosa before and during each cycle of therapy is shown in the last two columns of Table I. Figs. 3 and 4 show the histologic structure of the endometrium obtained by biopsy from Patient M. P. on the first and

fourteenth days, respectively, of an artificial cycle. Fig. 5 shows a mild degree of cystic glandular hyperplasia produced after the third attempt to produce withdrawal bleeding in Patient M. M. The total dose of diethylstilbestrol used for this cycle was 70 mg. These histologic findings are in agreement with the report of Wenner and Joël,[4] that more than 60 mg. of diethylstilbestrol may produce hyperplasia. Forty-two milligrams have been an optimum dose of diethylstilbestrol for the production of normal endometrial proliferation in fourteen days. Estrogenic hormone was absent from the urine of the 4 patients listed in Table I when treatment was

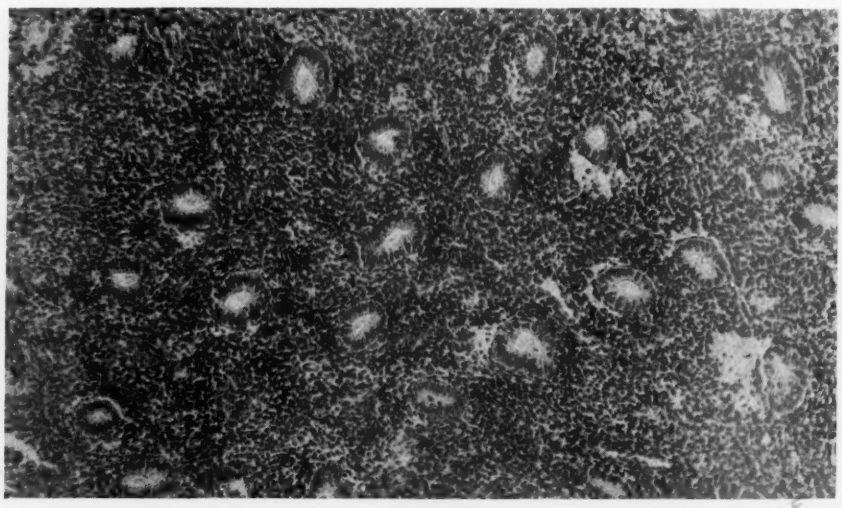

Fig. 3.—Photomicrograph of inactive endometrium obtained at the beginning of an artificially produced threshold cycle in Patient M. P. (×120.)

Fig. 4.—Photomicrograph of normal proliferative endometrium obtained on the fourteenth day of an artificially produced threshold cycle in Patient M. P. A total dose of 42 mg. diethylstilbestrol was given. Bleeding occurred from this endometrium eleven days later (×120).

started. To date there has been no spontaneous occurrence of menstruation following substitution therapy, other than the immediate withdrawal bleeding.

Variations in the administration of diethylstilbestrol were tried in 4 postmenopausal patients whose pelvic organs were intact (Table II). It is noted (1) that the lengths of the artificial estrogenic cycles varied with the duration of therapy when the daily dose was 1 or more mg.; (2) that when the daily dose was decreased to 0.1 to 0.3 mg. bleeding occurred during therapy although the latent interval between the fall of daily dose and the onset of bleeding was prolonged; (3) that the latent interval between complete cessation of therapy (when the daily dose was 1 mg. or more) and the onset of bleeding was consistently five to six days; and (4) that the pH of the vagina was lowered in every instance following estrogen therapy.

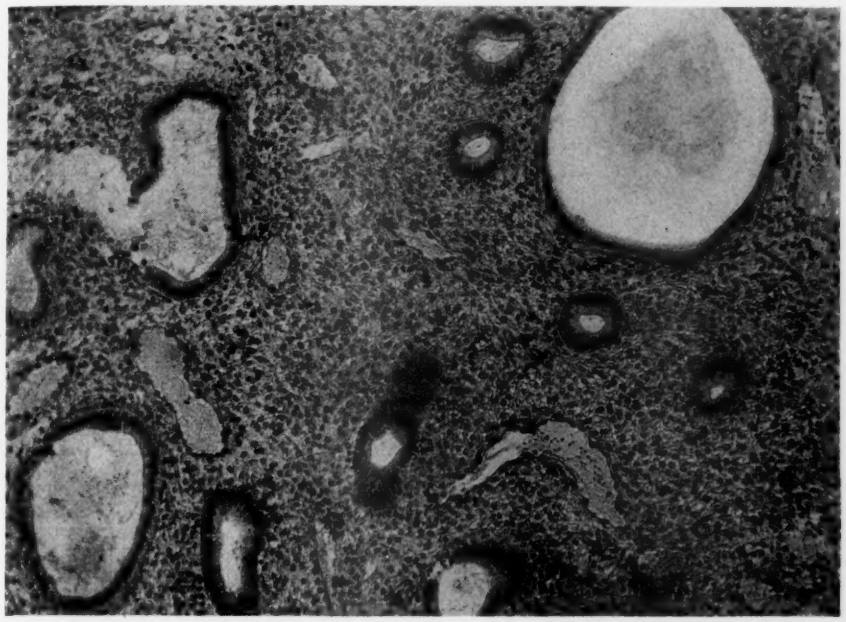

Fig. 5.—Photomicrograph of cystic endometrium obtained from Patient M. M., after a total oral dose of 70 mg. diethylstilbestrol in fourteen days. (×120.)

DISCUSSION

The purposes for which the clinical experiments reported in this paper were intended are: (1) To ascertain the oral therapeutic dose of diethylstilbestrol necessary for the production of normal endometrial proliferation and estrogen-withdrawal bleeding in women without ovarian function. (2) To estimate the amount of diethylstilbestrol administered by mouth over a period of fourteen days which would produce abnormally hyperplastic endometrium. (3) To produce, by cyclical estrogen therapy, artificial menstrual cycles in women according to Zuckerman's interpretation of "threshold cycle" as it pertains to the monkey. (4) To demonstrate the presence or absence in the human being of a *fluctuating* uterine threshold to diethylstilbestrol.

It is admitted, for the present, at least, that probably there is no particular reason for inducing uterine bleeding by substitutional therapy. However, definite growth of the uterus and development of

TABLE I*

PT.	DIAGNOSIS OF AMENORRHEA	AGE	NO. OF CYCLE	TREATMENT (DIETHYLSTILBESTROL)	LENGTH OF CYCLE DAYS	LATENT INTERVAL BET. CESSATION OF TREATMENT AND BLEEDING	VAGINAL pH	
							BEFORE TREATMENT	DURING TREATMENT
M. P.	Primary (genital hypoplasia)	16	1	42 mg. in 14 days	20	6 days	6.0	4.0 4.0
			2	7 mg. in 7 days	–	No bleeding	4.8	– –
			3	42 mg. in 14 days	20	6 days	4.8	4.0 4.0
			4	42 mg. in 14 days 0.3 mg./day 15th-22nd day	25	3 days	5.2	4.0 4.0
			5	42 mg. in 14 days 0.1 mg./day 15th-22nd day	21	Bleeding 22nd day during treatment	–	4.0 –
G. A.	Primary (pituitary infantilism)	24	1	42 mg. in 14 days	–	No bleeding	6.0	4.4 4.0
			2	42 mg. in 14 days	19	5 days	4.8	4.0 4.0
			3	42 mg. in 14 days	19	5 days	4.4	– –
			4	19 mg. in 19 days	24	5 days	–	4.0 –
D. S.	Primary (genital hypoplasia)	18	1	7 mg. in 7 days	–	No bleeding	7.6	– –
			2	7 mg. in 7 days	–	No bleeding	6.8	5.2 –
			3	52 mg. in 14 days 0.3 mg./day 15th-22nd day	21	Bleeding 22nd day during treatment	6.0	4.0 –
M. M.	Primary (genital hypoplasia)	20	1	42 mg. in 14 days	–	No bleeding	6.0	4.0 –
			2	42 mg. in 14 days	–	No bleeding	5.6	4.0 –
			3	70 mg. in 14 days	19	5 days	5.6	4.0 –

*Data pertaining to threshold cycles produced artificially in the human being with diethylstilbestrol.

TABLE II*

PT.	DIAGNOSIS OF AMENORRHEA	AGE	NO. OF CYCLE	TREATMENT (DIETHYLSTILBESTROL)	LENGTH OF CYCLE DAYS	LATENT INTERVAL BET. CESSATION OF TREATMENT AND BLEEDING	VAGINAL pH	
							BEFORE TREATMENT	DURING TREATMENT
I. O.	Secondary (natural menopause 5 years)	58	1	38 mg. in 21 days	24	4 days	5.6	4.8 –
			2	21 mg. in 21 days	–	No bleeding	5.6	5.2 –
			3	5 mg. in 1 day	6	5 days	5.6	4.4 –
J. D.	Secondary (natural menopause 30 years)	81	1	14 mg. in 14 days	19	5 days	7.2	– –
			2	14 mg. in 14 days	20	6 days	–	6.8 –
			3	49 mg. in 14 days	19	5 days	–	4.8 –
			4	42 mg. in 21 days	27	6 days	–	– –
J. N.	Secondary (natural menopause 6 years)	52	1	21 mg. in 21 days	–	No bleeding	7.6	4.4 5.2
			2	2.8 mg. in 14 days	–	No bleeding	5.2	4.0 –
			3	42 mg. in 14 days	20	6 days	5.0	4.0 4.0
			4	23 mg. in 23 days	28	5 days	5.6	4.0 5.0
			5	36 mg. in 18 days 0.1 mg./day 19th-31st day	30	Bleeding 31st day during treatment	–	4.8 4.8
V. N.	Secondary (natural menopause 5 years)	44	1	21 mg. in 21 days	26	5 days	5.0	4.4 –

*Data pertaining to threshold cycles produced artificially in the human being with diethylstilbestrol.

other secondary sexual characteristics were effected by cyclical estrogen therapy along with periodic uterine bleeding. There is considerable experimental evidence that prolonged uninterrupted estrogen treatment produces undesirable results that are not produced by cyclical therapy (Palmer[1]).

The importance of cyclical estrogen therapy has been revealed by an investigation of the case history of Patient M.P. (Table I). For seven and one-half months this patient received thrice-weekly injections and oral doses of one estrogen or another without periods of observation for withdrawal bleeding. Efforts had been directed toward the development of mammary tissue for cosmetic reasons and the establishment of the menarche. Withdrawal bleeding of two days' duration occurred finally six days after the cessation of the long uninterrupted course of estrogen therapy. Following the first attempt at cyclical therapy, withdrawal bleeding occurred six days after a threshold cycle of diethylstilbestrol, and endured four days.

SUMMARY

1. Zuckerman's experimental data on the production of artificial menstrual cycles and a fluctuating uterine threshold to estrone in the monkey are reviewed.

2. Artificial menstrual cycles (diethylstilbestrol withdrawal bleeding) were induced by cyclical diethylstilbestrol therapy in 4 patients with primary amenorrhea and in 4 postmenopausal women.

3. Forty-two milligrams were found to be an optimum oral dose of diethylstilbestrol which in fourteen days would produce a normal degree of endometrial proliferation and would be followed by uterine bleeding.

4. Seventy milligrams of diethylstilbestrol by mouth in fourteen days produced a slight degree of cystic glandular hyperplasia of the endometrium.

5. The consistency of the latent interval that precedes withdrawal bleeding in the group of primary and postmenopausal amenorrheic patients, regardless of variation in dosage and manner of administration, leads one to believe that a *fluctuating* uterine threshold to estrogen may not be a factor with which to be concerned as it will be shown to be in patients with uterine bleeding (Palmer[2]), and as it is known to be in the ovariectomized monkey.

The diethylstilbestrol used in this investigation was supplied by the Eli Lilly and E. R. Squibb Companies.

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(A second contribution to this subject will appear in the June issue of the Journal.*)*

THE PRESENCE OF EXCESSIVE AMOUNTS OF GONADOTROPIC PRINCIPLE IN THE URINE OF PATIENTS WITH THYROID DISEASE

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AMONG myxedematous women, Zondek[1] only infrequently found an increased urinary output of the gonadotropic principle. Among five women with severe exophthalmic goiter, he found only one who had an increased output of the gonadotropic principle. Our interest in the relationship of thyroid dysfunction to the function of gonadotropic principle was stimulated by observations made in the case which follows:

REPORT OF CASE

An unmarried woman, 35 years of age, came to the Mayo Clinic in April, 1937, and was dismissed in August, 1938. This patient was concerned about a goiter, the presence of which first had been noted ten years earlier and which had been gradually growing to its present size. She also was concerned about gradually increasing nervousness, palpitation, weakness, and loss of weight, which had been progressively worse for two to three years. Since the menarche at twelve years of age, the menses seldom appeared oftener than once a year. The right eye had been noticeably more prominent than the left for an unknown length of time. These difficulties had never been incapacitating.

On admission, the patient weighed 131 pounds (59.4 kg.). The blood pressure, measured in millimeters of mercury, was 110 systolic and 64 diastolic; the pulse rate was 73 beats per minute. The thyroid was diffusely enlarged; each lobe measured about 1 by 2 inches (2.5 by 5 cm.). There was a moderate degree of lag and retraction of the right eyelid. The left eye appeared normal. Pelvic examination gave negative results. The basal metabolic rate was normal.

Thyroidectomy was considered but never urged. Since the patient volunteered a decided unwillingness to consider such a procedure, medical treatment was instituted. Lugol's solution, 10 drops three times a day, was given. Because of the amenorrhea, one of us (D. G. D.) had the urine assayed for the gonadotropic principle. Sixty-six rat units of gonadotropic principle and 20 R.U. of estrin were demonstrated per liter of urine (Fig. 1, *a* and *b*). The patient was under observation for about sixteen months. In this time the basal metabolic rate gradually fell to -17 per cent and the weight on dismissal had increased to 151 pounds (68,5 kg.). At dismissal, the gonadotropic principle was not demonstrable in the urine. The thyroid may have become a little larger and was definitely softer in consistency than on admission. There was no striking improvement in the exophthalmos as measured by the exophthalmometer, but the edema and retraction of the lids had become less noticeable. The patient's general health was subjectively improved. During all this period of observation her symptoms never interfered with continuous employment as a domestic.

This study has been made in an attempt to demonstrate what influence, if any, thyroid disease has on the urinary output of gonadotropic prin-

ciple. Assays of 101 specimens of urine from 63 patients suffering from various thyroid diseases were made for the gonadotropic factor.

PROCEDURE

The Selection of Patients.—Since we lacked precedent, the urinary output of gonadotropic principle of all patients with thyroid disease was studied at first. A total of 63 patients were examined. Because excessive amounts of the gonadotropic principle are excreted during the menopause, we decided to exclude from this study the data obtained on all women forty years of age or more. There were 10 such patients. We

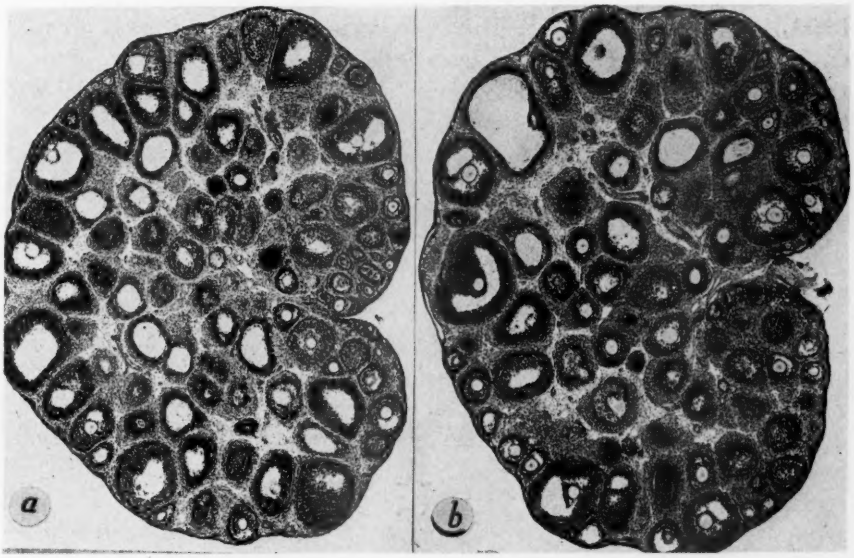

Fig. 1.—Sections of ovaries from rats used for assay of gonadotropic principle: *a*, control; *b*, from litter mate of rat used for control, after injection of urine from a woman aged 35 years, with exophthalmic goiter; assay indicates presence of 66 R.U. of gonadotropic principle per liter.

are reporting, therefore, the results obtained from examination of 53 patients: 22 men and 31 women. These patients had a variety of thyroid diseases or dysfunctions. The ages of the males ranged from 19 to 60 years; of the females from 8 to 39 years.

The Selection of Controls.—There are numerous accounts in the literature of quantitative determinations for the gonadotropic principle in the urine of normal individuals.

Comparison of our data with that from these sources proved difficult, partly because the methods of assay were not always identical with ours and partly because the series of cases was sometimes rather small. Osterberg and one of us (Drips[2]), who described the method of assay employed in this study, examined the urine of 13 healthy, normally menstruating young women. Their data have been utilized as our control study for the excretion of gonadotropic principle by women. To supplement this series we analyzed 17 twenty-four-hour specimens of urine

from 10 men. Three of these men were hospitalized patients who had received surgical treatment for an injured tendon of hand, tuberculosis of spine, and inguinal hernia, respectively. The others were physicians who were in good health.

The Method of Assay.—Twenty-four-hour specimens of urine were collected. Four hundred cubic centimeters of the specimen were concentrated for gonadotropic principle according to Frank's acetone method. This method makes use of the fact that gonadotropic principle is precipitated out of the urine on addition of acetone. The hormone-containing precipitate is extracted. The extract is adjusted to an optimal pH and a volume of 8 c.c. so that the gonadotropic principle in the extract is 50 times more concentrated than in urine. This material is assayed on immature rats as has been described.[2] These investigators accepted the presence of stimulation of the ovarian follicles viewed in serial sections as evidence of the presence of the gonadotropic principle in the urine. The yield of gonadotropic principle is expressed in terms of rat units per liter of urine. In nearly every case an effort was made to demonstrate yields of 25, 40, and 66 R.U. per liter of urine.

THE DATA

The Excretion of Gonadotropic Principle by Normal Individuals.—None of the thirteen young, healthy, normally menstruating women observed by Osterberg and one of us (Drips) excreted more than 20 R.U. per liter. In our studies of the urine excreted by normal men we found 20 R.U. of gonadotropic hormone per liter excreted on only one occasion by one person. A second specimen yielded 10 R.U. per liter and a third specimen from this subject failed to reveal any gonadotropic principle. All assays of urine from the other normal men revealed less than 20 R.U. of gonadotropic principle or none at all. On the basis of these data, it would seem that normal individuals may excrete as much as 20 R.U. or less of gonadotropic principle per liter of urine. This variation in excretion compares favorably with the findings of other investigators. There are not enough data at hand to tell us how often normal individuals excrete more than 20 R.U. per liter of urine.

The Excretion of Gonadotropic Principle in the Urine of Patients With Thyroid Disease.—A summary of our observations is given in Table I. The patients were grouped according to type of thyroid disease and sex. The yield of gonadotropic principle was assigned in accordance with an arbitrary quantitative division or grouping (Table I). A yield of 25 R.U. or more is probably definitely excessive. Therefore this division was used. In the first group are all yields of 24 R.U. per liter or less; in the second group, all yields of 25 to 40 R.U. per liter; and in the third group, all yields of 40 R.U. or more. Assay of more than one specimen of urine was obtained in some cases, but only the report of the first assay has been utilized for the data in Table I. Sections of ovaries from rats used in assay of gonadotropic principle in two cases are presented in Figs. 2, *a* and *b* and 3, *a* and *b*.

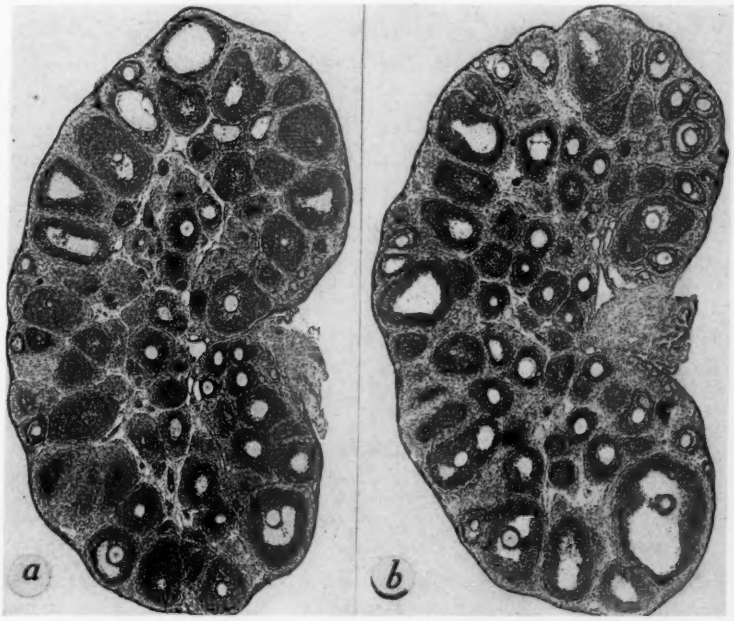

Fig. 2.—Ovaries from rats: *a*, control; *b*, from litter mate of rat used for control after injection of urine from woman aged 29 years, with exophthalmic goiter; assay indicates 66 R.U. of gonadotropic principle per liter of urine.

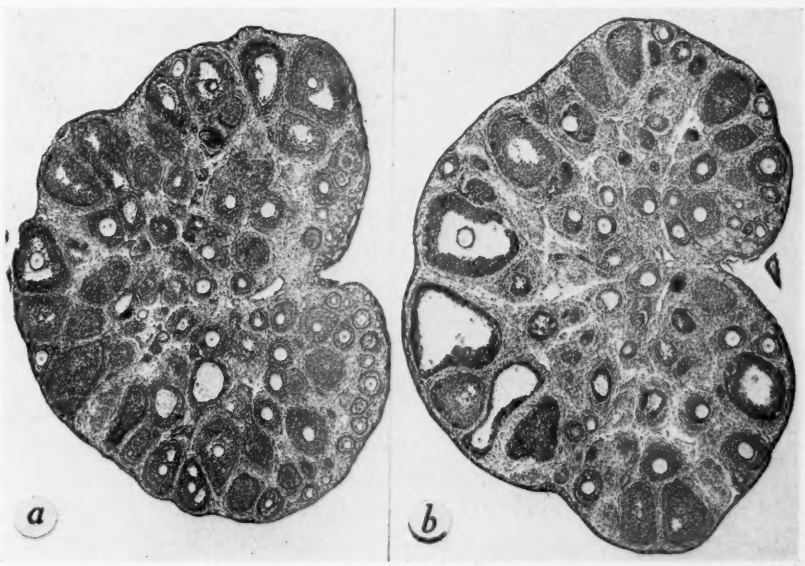

Fig. 3.—Sections of ovaries from rats used for assay of gonadotropic hormone: *a*, control; *b*, from litter mate of rat used for control after injection of urine from a man, aged 38 years, with exophthalmic goiter; assay indicates 66 R.U. of gonadotropic principle per liter of urine.

COMMENT

This study was undertaken to determine whether thyroid disease was a factor in the excretion of the gonadotropic principle and particularly in the excretion of increased amounts. In analyzing the case histories an attempt was made to select such data as might have some actual or theoretical bearing on the output of gonadotropic principle. Thus, we made note not only of the patient's age, sex, and type of thyroid disease, which are indicated in Table I, but also the duration of the thyroid disease, the height of the basal metabolic rate, the catamenia and the history of using iodine (excluding the possible use of iodized salt).

TABLE I. GONADOTROPIC PRINCIPLE IN URINE IN 53 CASES OF THYROID DISEASE

DISEASE	TOTAL CASES	RAT UNITS PER LITER OF URINE		
		24 OR LESS	25 TO 40	40 OR MORE
Males				
Exophthalmic goiter*	16	12	3	1
Exophthalmic goiter with adenoma*	4	3		1
Exophthalmic goiter suspected	1	1		
Myxedema	1		1	
Females				
Exophthalmic goiter*	16	11		5
Adenomatous goiter with hyperthyroidism*	5	3		2
Adenomatous goiter without hyperthyroidism*	2	2		
Exophthalmic goiter suspected	5	2	1	2
Myxedema	2		1	1
Artificial hyperthyroidism	1	1		
Male	22	16	4	2
Female	31	19	2	10
Total	53	35	6	12

*Diagnosis proved at operation.

Within the limitations of this study no definite correlations were found. Certain evidence, however, is clear. The type of thyroid disease, such as exophthalmic goiter, adenomatous goiter, or myxedema, does not determine that the urine will contain large amounts of the gonadotropic principle. Similarly, large amounts are present in the urine of patients of both sexes with thyroid disease and in the urine of patients who have low as well as those who have elevated basal metabolic rates. In the presence of thyroid disease urine voided at any time in the menstrual cycle may contain large amounts and women with normal as well as irregular menstrual periods are capable of excreting increased amounts. It is impossible to say what effect age has on this phenomenon. It is notable, however, that one girl, eight years of age, who had exophthalmic goiter, excreted excessive amounts. All the men who excreted 25 R.U. or more of gonadotropic principle per liter of urine were less than fifty years of age. Among women use of iodine might be a possible factor in suppressing the excretion of excessive amounts of gonadotropic prin-

ciple. We have observed that the excretion of gonadotropic principle may vary considerably in amount from day to day in the same individual.

On the basis of this study it is not possible to explain why some patients with thyroid disease excrete excessive amounts of gonadotropic principle and others do not.

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CLINICAL EXPERIENCE WITH PREGNENINOLONE*

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IN 1938 Inhoffen and Hohlweg,[1a] by adding the ethynil radical to estradiol, produced the synthetic estrogen ethynil estradiol. This substance was remarkable in that it was very effective when given by mouth, but it had too many undesirable side-actions for clinical use. These same workers added the ethynil radical to testosterone, and presented a new synthetic product called variously △ 4-pregnene-:n, 17-ol, 3-one, ethynil testosterone, anhydro-oxy-progesterone, or pregneninolone.[1] In this paper it will be called pregneninolone. It was unique in having a marked corpus luteumlike effect upon the endometrium of rabbits when given orally. Even pure progesterone, generally considered to be the corpus luteum hormone, has no appreciable action when given orally.[1] Yet it was shown that the minimal effective dose of pregneninolone in immature female rabbits (first "primed" with estrogen) was only 4 mg., while 60 mg. of progesterone orally had no effect. Clauberg and Üstün[8] and Salmon, Walter, and Geist[6] have shown that in postmenopausal patients a secretory endometrium ensues when estrogenic therapy is followed by 300 to 500 mg. of pregneninolone orally. Hamblen and co-workers[11] have reported the production of a secretory type of endometrium in irregularly menstruating women with pregneninolone. Zondek and Rozin[9] were able to induce bleeding in a normally menstruating female in midcycle with 280 mg. of this substance given orally, an effect which also followed the injection of 50 mg. of progesterone.[9, 10] They also induced bleeding in secondary amenorrhea with 300 mg. of pregneninolone by mouth, but not after only 220 mg.[9] Courrier and Jost[2] have maintained pregnancy in rabbits castrated during pregnancy with oral pregneninolone.

Because of the possibility of obviating costly and time-consuming injections of progesterone, and also because of the academic interest

*The generous supply of pregneninolone was furnished by the Ciba Pharmaceutical Products, Inc.

in this substance which apparently possesses progestational, estrogenic, and androgenic activity[3] (see discussion), we have used pregneninolone clinically during the past twelve months. Experimental data obtained with rabbits and rats appear in another report (in press).

The 28 female patients comprising this study were seen both in private practice and in the Evanston Hospital Out-Patient department. Oral pregneninolone was employed in the treatment of unexplained or "functional" endocrine disorders. All known local or systemic factors, such as genital pathology or thyroid deficiency, which might have been of etiologic significance were ruled out. Usually other types of endocrine therapy had been tried first without the desired effect. A summary of clinical data is included in tabular form (Table I).

TABLE I. SUMMARY OF CLINICAL DATA

CASES	COMPLAINT	DOSE	RESULTS
6	Menorrhagia	200-1,140 mg. in 14 premenstrual days	No beneficial effects
2	Premenstrual tension	210-270 mg. in 14 premenst. days	Excellent in one Variable in one
6	Dysmenorrhea	210-560 mg. in 14 premenst. days	Excellent in one Variable in four Worse (?) in one
4	Secondary amenorrhea	230-300 mg. in 14 days or less	Bleeding after each trial of medication
3	Threatened abortion	40 mg. daily for 2 days, 3, and 12 days	2 aborted. 1 delivered at term, after 5 weeks of spotting in the third and fourth months
2	Sterility	40 mg. daily for 14 premenst. days. 20 mg. (same)	Secretory endometrium Early secretory endometrium No pregnancies
2	Menopausal symptoms	30 mg. daily for 12 days	Beneficial (?) in one No effect in one
3	Nausea of pregnancy	20-40 mg. daily	Dubious effect in all

It has not been possible always to predict the effect, if any, of pregneninolone from month to month, even in the same patient. This was especially true in the treatment of dysmenorrhea—a complaint in which psychic and environmental factors are notoriously difficult to evaluate. Occasionally the results of therapy were striking, but in most cases the substance was of very dubious value.

Of particular interest were 4 cases of secondary amenorrhea. Since the history and response to therapy of each were similar, one summary will suffice:

M. M., first seen in November, 1939, at 23 years of age, had had but 6 episodes of vaginal bleeding since the menarche at 16. About every thirty days she would have a feeling of pelvic congestion and fatigue, but usually had no menstrual flow. Her past history was essentially negative, and for the past twelve months her basal metabolic rate had been maintained at 0 to +12 per cent with 2 gr. of desiccated thyroid daily, with no change in her menstrual history. Previous to

thyroid therapy her basal metabolic rate had been –18 per cent and –21 per cent. Pelvic findings were not unusual. The cervix appeared and felt normal; the corpus uteri was anterior, small, but not infantile. The adnexa felt normal by bimanual palpation, though the right ovary had been reported fourteen months previously as "slightly enlarged" by another doctor. Her weight was consistently 155 to 160 pounds, height was 5 feet 9 inches, contours and hair distribution were of the feminine type, and her mental adjustment to her life was good. Her only complaints were that she "wanted to be like other girls," that she wanted a family after marriage, and that she "felt better after menstruating."

An endometrial biopsy at this time showed a thin "resting" type of endometrium. In January, 1940, she began to bleed on the thirteenth day of medication, after having taken a total of 270 mg. of pregneninolone by mouth. This flow lasted for five days. Likewise, in February, 1940, three days after 260 mg. in twelve days, she had a four-day flow. For the next three months, she received no medication, and had no bleeding. In June she had two days of vaginal bleeding, beginning on the twelfth day of therapy, after a total of 230 mg. of pregneninolone. Again in July, after 280 mg. of pregneninolone in ten days, she bled for three days. An endometrial biopsy on the first day of this bleeding was of an early secretory, or progestational type. In August, bleeding occurred on the eleventh day of therapy, after 300 mg. of pregneninolone; the biopsy on the first day of flow was also of an early secretory phase of the endometrium.

TOXICITY

We were especially interested in the possible toxicity of this new substance. When the ethynil radical was added to estradiol, the oral effectiveness of this estrogen was greatly enhanced (16 times),[1] but there were many unpleasant side actions in the human being, chiefly referable to the gastrointestinal tract. There has been only one report to date of the toxic effects of pregneninolone; and the doses used, experimentally and clinically, were not large. Hamblen and co-workers[11] have given comparatively very large doses, as high as 2,280 mg. in fourteen days, and we have used up to 1,140 mg. in fourteen days without untoward effects. None of our patients voluntarily complained of any distress, and when questioned, offered no definite evidence of variation from previous states of health. One of us ingested 270 mg. of pregneninolone at one dose and experienced no symptoms. In 81 experimental animals which were being studied concomitantly, the livers, kidneys and adrenal glands were examined grossly and histologically. There were no pathologic changes in these pregneninolone-treated animals. By limiting their water supply to one containing a suspension of the pure crystals, two rats were induced to take the relatively tremendous doses of 655 and 730 mg. of pregneninolone in twelve and eighteen days, respectively. The first animal was killed at the cessation of treatment, and the other three weeks after medication was stopped. Neither showed gross or histologic evidence of damage to the above list of essential organs.

DISCUSSION

Pregneninolone has been given by the oral route to 28 female patients presenting complaints in which progesterone therapy is thought by many to be beneficial. That the results of this therapy have not been encouraging is admittedly due in part to the difficulty of treating disorders whose etiology is so largely a matter of conjecture. From experimental evidence one cannot conclude that pregneninolone's ac-

tions are identical throughout with those of progesterone. One usually considers the sex hormones, all of which are chemically related sterols, to be divided into 3 distinct groups: estrogenic, androgenic, and progestational. The estrogens provoke estrus changes in the female genital tract, or those changes occurring during the follicular phase of ovarian activity, such as a proliferative type of endometrium and cornification of the vagina. Androgenic substances stimulate male sexual structures, for example, the prostate, seminal vesicles, penis, and cock's comb. Progestational changes are found during the life of the corpus luteum, and include the secretory phase of the endometrium, decidua formation, mucification of the rat vagina, and allegedly, depression of uterine irritability. In general, these sex hormones exhibit a special predilection for specific reproductive structures. Possibly because the molecular structures of these sex-sterols are very similar, there is some overlapping of biologic effect, especially when large doses are used. To cite but two of many examples, large doses of progesterone produce definite androgenic effects,[12] while certain doses of androgens as well as estrogens will cause growth,[13] edema and hyperemia[14] of the rat uterus.

Emmens and Parkes[3] first noted that pregneninolone not only had progestational activity, but also produced signs of estrogenic stimulation in the rat vagina, and evidence of androgenic stimulation in the cock's comb. Courrier and Jost[2] observed androgenic changes in the castrated rat and chick's comb with pregneninolone. One of us (E. S. B.) has also obtained these apparently conflicting effects in experimental animals, as well as additional evidence that pregneninolone and progesterone are not biologically identical.

It has been tempting to hypothecate that pregneninolone during the process of digestion and absorption is converted into the chemically very similar progesterone. Yet histologic studies of pregneninolone-treated animals are not completely similar to those observed under progesterone treatment. Furthermore, the physiologic responses of the uteri of rabbits treated in vitro with the 2 substances are quite different, i.e., progesterone-treated uteri do not react to relatively large amounts of oxytocics, such as pituitrin, while pregneninolone-treated uteri manifest a marked increase in uterine tone and magnitude of contraction when pituitrin is given. This observation alone should provoke much hesitation before employing in threatened abortion a substance acting differently from the frequently recommended progesterone.

The use of pregneninolone to produce bleeding in secondary amenorrhea probably amounts to more than crude empiricism. Since, in the 3 cases presented, there were no objective signs of estrogenic deficiency except amenorrhea, one must assume that enough estrogen was present to prevent other signs of estrogen-lack (such as vulvar, vaginal, uterine, or breast atrophy). It is known that small amounts of estrogen potentiate the action of progesterone upon sexual structures. It is, therefore, theoretically possible to produce a progestational endometrium with a substance such as pregneninolone which has some progestational properties and to obtain bleeding from this "prepared" endometrium.

SUMMARY AND CONCLUSIONS

1. Pregneninolone, a new synthetic product, when given orally produces a progestational type of endometrium.

2. It has no detectable toxic effects in laboratory animals or in the human being when given in the relatively large doses used in our studies.

3. In general, it has not been of clinical value. Its possible mode of action in producing bleeding in secondary amenorrheics has been discussed.

4. It cannot be considered to have effects identical with those of progesterone.

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OBSERVATIONS ON THE EFFECTS OF PENTOBARBITAL SODIUM (NEMBUTAL) ON THE INTACT UTERUS OF ANIMALS*

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THE prominent role occupied by the barbiturates for analgesia during labor is evident from the reports of Averett,[1] Clifford and Irving,[2] Galloway and Smith,[3] Jones,[4] Kane and Roth,[5] King,[6] and many others. Among the barbiturates used, pentobarbital sodium (nembutal) has no doubt been administered most extensively and successfully. Two outstanding experimental works are those of Adair and Pearl[7] and Gruber.[8] Recently Tatum[9] has thoroughly reviewed the present status of the barbiturates. Since so much interest in nembutal is manifest, further experiments on intact uteri of some laboratory animals were considered worth while.

METHODS

The animals used in the experiments were for the most part rabbits, supplemented by guinea pigs, cats, and dogs. Twenty-five animals were used, most of them in the latter part of pregnancy. A few post-partum rabbit uteri were studied. The breeding dates of all the pregnant rabbits were known, and the other animals were

*The nembutal was kindly furnished by the Abbott Laboratories.

all near term. Each animal was prepared for experimentation after the method of cerebral anemia suggested by Swenson[10] and used in a previous investigation published by Mitchell and Pankratz.[11] Under light ether anesthesia both common carotid arteries were quickly ligated and usually a heavy ligature was tied around the entire neck musculature, sparing the vagi and trachea. The trachea was cannulated and no further anesthetic was used. Animals were then strapped to a special aluminum board and the uterus exposed through a midline incision. This procedure usually took only about ten minutes.

A thread for recording was tied into the serosa of a suitable uterine segment, in an area not over the placenta and rather avascular. The entire lower half of the animal fastened to the animal board was then immersed in a large bath of mammalian Ringer's solution. This solution was kept at a constant temperature of from 37.5° to 38.5° C., and stirred mechanically. The uterine segment to which the thread was attached was free in the bath except for its anatomic anchorage. Care was taken to preserve the blood supply of uterine segments studied. Kymographic records were made by means of a heart lever attached directly to the thread.

Animals thus prepared were observed for three to seven hours, without difficulty. A control record of uterine activity was usually made for one hour or until a typical contraction record was obtained. During a previous series of experiments,[11] we had observed that the rabbit, the guinea pig, the cat, and the dog each had a definite uterine contraction pattern. Veterinary nembutal was administered on a weight basis, 0.1 c.c. (0.1 gr.) for each pound of animal weight. This dosage is recommended as a surgical dose. In all of our experiments two or three such doses were given at intervals varying from one to three hours. The nembutal was given either subcutaneously or intramuscularly. No difference was observed in the two methods, except that the latter was quicker. The effectiveness of the nembutal was checked by either pulling on the peritoneum or pinching a foot, and by the respiration which became slower but even and usually deeper.

RESULTS

The normal uterine movements in all animals consisted of frequent circular contractions, and slower but more powerful longitudinal contractions. These could be easily distinguished both by the eye and by the character of the kymograph record.

PREGNANT RABBITS

The uteri of these animals were all quite active, the ones nearest term being most active. In all the experiments it seemed that as soon as the drug began to take effect the uterus would manifest an even and typical contraction pattern. The tracings shown in Figs. 1 and 2 were taken of a rabbit twenty-six days pregnant. This animal was observed for seven hours and during that time received 0.2 gr. of pentobarbital sodium per pound. The uterus was active and the animal in good condition at the end of the experiment.

POST-PARTUM RABBITS

Three rabbits were studied within one day after delivery and found to be very active. Fig. 3 is a kymograph record obtained from a doe that had delivered the day before the experiment. She was observed for over five hours and received subcutaneously 0.2 gr. of nembutal per pound in two doses within one hour.

The uterine contraction of four rabbits in estrus was also studied. Such uteri are less active as was pointed out in a previous publication.[11] The administration of nembutal in doses of 0.1 to 0.2 gr. per pound animal weight showed no definite suppression of uterine motility.

GUINEA PIGS

Only 3 guinea pigs were used, but these were near term. The first dose of 0.1 gr. of nembutal per pound caused no change in uterine contractions (Fig. 4), and

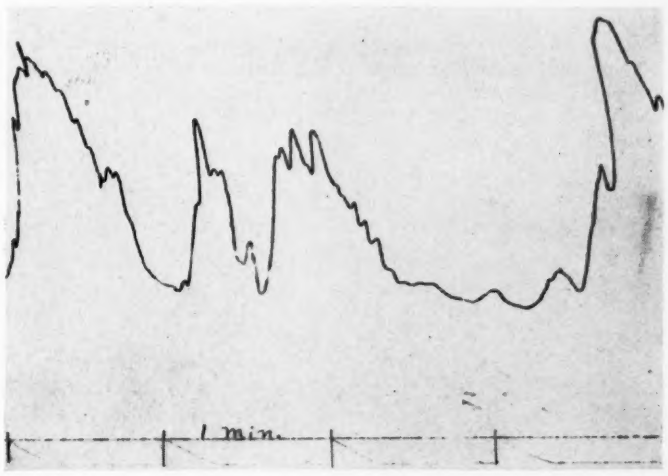

Fig. 1.—Tracing of uterine contraction in a rabbit twenty-six days pregnant. The record was made before any nembutal had been administered.

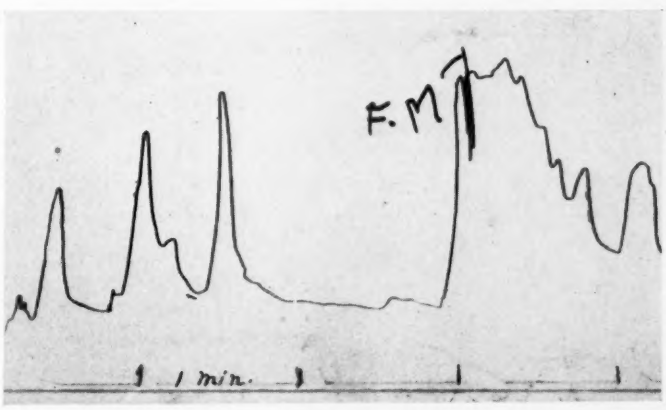

Fig. 2.—Tracing of uterine contractions in the same animal as shown in Fig. 1, but three hours later and soon after second dose of nembutal (0.1 gr. per pound). *F. M.*, indicates fetal movements in utero. Four fetuses were removed before this graph was made.

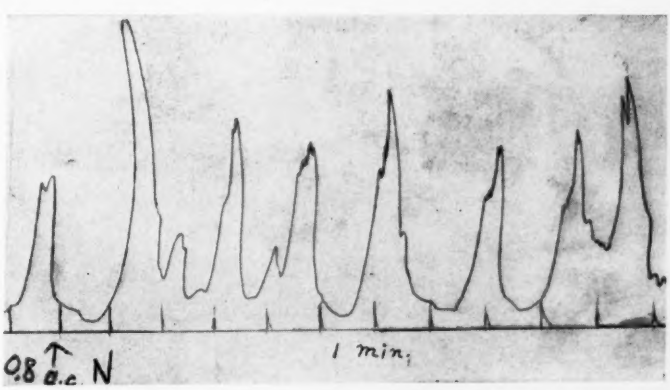

Fig. 3.—Tracing of uterine contractions in rabbit during the first day after delivery. Record made one hour after first dose of nembutal and at the time of second injection.

the fetuses remained active. But when a second similar dose was given an hour later, the fetuses first made kicking movements in utero, and then became inactive. A number of them died in utero, and at the end of the experiment it was found that the placentas were detached. The uterus continued to contract.

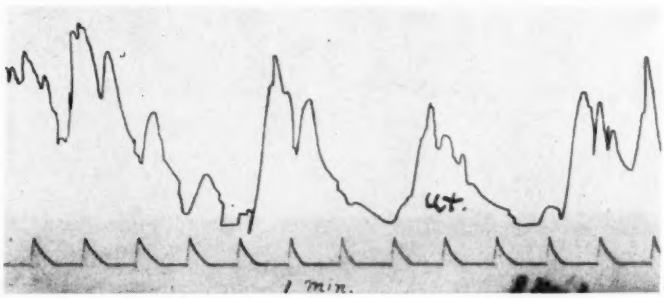

Fig. 4.—Tracing showing uterine contractions in the guinea pig near term. Record taken one and one-half hours after second dose of nembutal (each dose 0.1 gr. per pound).

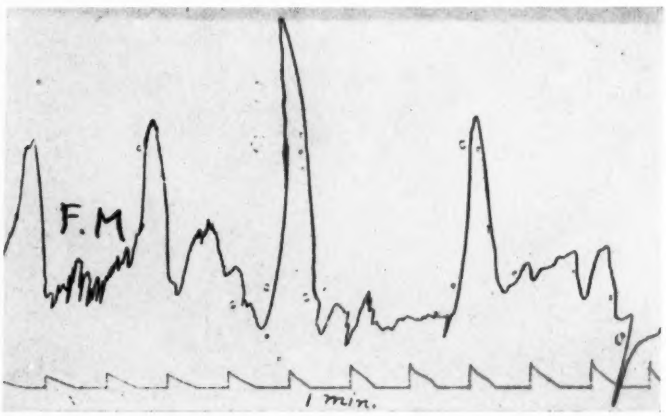

Fig. 5.—Tracing of uterine contractions in a cat near term. Record made three hours after the first injection and two hours after the second injection. *F. M.*, indicates fetal movements.

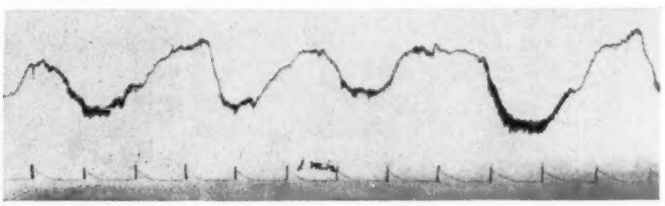

Fig. 6.—Tracing of uterine contractions in a dog near term. Record made two hours after the second injection of nembutal (0.1 gr. per pound, each dose). The small changes in the tracing are due to maternal respiration which is not depressed.

CATS

A small number of cats was used. Here again the first dose of 0.1 gr. of pentobarbital sodium per pound caused no change in uterine contractions or in the behavior of the fetuses (Fig. 5). A second similar dose within one hour caused the fetuses to kick in utero, the mother to breathe slower, but the uterus showed no

change. Fetuses removed after six hours were rather inactive and responded slowly to strong stimulation. In these, respiration was slow and irregular at first, but gradually improved. No fetuses died during any of the experiments.

DOGS

Only two dogs were used, one having 9 and the other 6 fetuses just at term. The uterus and fetuses of one animal were observed for seven and one-half hours. During the first four hours of the experiment, this dog was given three doses of pentobarbital sodium, a total of 0.35 gr. per pound of body weight. Four fetuses were removed about the middle of the experiment and five more at the end. All were alive and active.

The second dog was observed for five hours. She was given two doses, a total of 0.2 gr. of pentobarbital sodium per pound during the first hour. The uterus continued to contract actively (Fig. 6). At the end of the experiment six fetuses were removed, one of these dead. The others soon became active. One pup out of each litter was bottle fed and kept alive.

DISCUSSION

In most of these experiments I also studied the behavior of the fetuses. A series of cinematographs were made of the fetal behavior during the experiments. It was observed that a dosage of 0.1 gr. of pentobarbital sodium per pound body weight did not alter the fetal behavior; but repeated doses would cause suppression of reaction to stimulation, gasping movements in utero or in the bath, and sometimes violent kicking was seen. During many experiments active peristalsis was observed and a number of animals defecated into the bath. On a few occasions actual delivery of fetuses occurred. Some of the guinea pigs and dogs removed by sectioning the uterus during or at the end of the experiment were kept and bottle fed.

In the experiments where 0.2 or 0.3 gr. of pentobarbital sodium per pound was administered, the fetuses became quite inactive and did not respond normally to various stimuli. During such experiments the near-term fetuses were put into a box with a light over them and in a few hours they became active. No mothers died from nembutal given in this series of experiments. Following the larger doses a few fetuses died in utero during the experiment.

The results in these experiments confirm the findings of Adair and Pearl,[7] in that nembutal produced no appreciable change in uterine activity. The marked effect of nembutal on smooth muscle of the uterus, noted by Gruber[8] was not observed. Unusual restlessness was not seen in any animals following various doses of nembutal. However this may be due to the fact that the series was not larger.

CONCLUSIONS

1. One dose of pentobarbital sodium (0.1 gr. per pound) did not cause a decrease in the tonus or the contractions of the uterus, when this viscus was kept relatively intact in the animal.

2. Fetuses remained active and responded to light stimulation with such a dosage.

3. Doses two and three times as large (0.2 to 0.3 gr. per pound), administered during a period of one to three hours, caused very little

change in uterine contractions, but did slow the maternal respiration and suppressed fetal activity considerably.

4. Fetuses removed after the larger doses did not respond normally to stimulation and showed definitely depressed respiration.

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MALARIA COMPLICATING PREGNANCY

With a Report of 27 Cases

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During the past twenty years in the city of Augusta, Georgia, of rather stable population of 65,000, 58 per cent of which are Caucasian and 42 per cent negro, there were approximately 27,300 live births, about 16,000 white and 11,300 negro. Among these were collected reports of 27 cases of malaria complicating the pregnancy. Twenty-two were in white and 5 in negro women. Most of the cases occurred in the 4 months of August, September, October, and November, each having from 4 to 7 cases. June and July had 2 and 3 cases, respectively, and the other months had one or none.

Age.—The youngest patient was a negress 15 years old and five months pregnant. She had 3 chills, recovered, and went home undelivered. Ten patients were under 21 years, 10 were 21 to 26 years of age and the others, all white, were 28, 32, 34, 35, 37, and 38, and the oldest 41 years of age.

Month of Gestation.—Two were in the first trimester, 8 in the second trimester, and 17 in the third trimester. All of this last group except one were eight months or more.

Type of Malaria.—Thirteen were tertian, 11 estivo-autumnal, 1 quartan, and 2 not determined because of incomplete records.

Symptoms.—Twenty patients had history of one to many chills, in some cases at very regular intervals. Many had malaise, headache, and dizziness. Few had vomiting and fainting attacks. Fever ranged from 100° to 105° F., but in each case it was promptly reduced by quinine therapy. One white woman near term was in coma for forty-eight hours and died. One negro woman in coma lived. In several patients, there was a marked degree of jaundice, and a large spleen was noted in many cases. Anemia by nature of the disease is common. Four patients had 1,000,000 red blood cells per cubic millimeter, 3 patients 2,000,000, and 2 only had more than 4,000,000 each. Leucopenia is also common. One patient had 3,000 to 4,000 white blood cells per cubic millimeter, 3 patients had 4,000 to 5,000, 2 patients 5,000 to 6,000, 2 patients 6,000 to 7,000, 2 patients had 7,000, one 8,000, two 9,000, three 10,000, two 11,000, one 12,000, one 13,000, and one 19,600. The hemoglobin corresponded with the number of red cells in each case. One had 10 per cent, one 20 per cent, one 30 per

cent, one 40 per cent, three 50 per cent, four 60 per cent, six 70 per cent, and four 80 per cent in those recorded. More than one-half of the patients had albuminuria, usually in slight degree.

Therapy.—Almost all of the patients were treated with quinine, and it is of interest to note the oxytocic effects, if any, of quinine. The usual dosage was 20 to 30 gr. daily. The following 7 patients had large doses of quinine up to 300 gr. and not under 80 gr. without inducing labor:

1. Gravida, 6 months, 130 gr. in 7 days during attack of malaria. No abortion.
2. Gravida, 8 months, 180 gr. in 6 days. No premature labor.
3. Gravida, 5 months, 80 gr. in 8 days. No abortion.
4. Gravida, 6 months, 185 gr. in 9 days. No abortion.
5. Gravida, 7 months, 150 gr. in 5 days. No premature labor.
6. Gravida, 8 months, 200 gr. in 2 weeks without onset of labor.
7. Gravida, 8 months, 120 gr. and went home, recovered without onset of labor.

The subsequent patients were the only ones who had been administered quinine prior to the onset of labor, premature or at term:

1. Gravida, 8½ months, 80 gr. in 12 days. Premature labor, infant weighed 5 pounds 1 ounce.
2. Gravida, 8½ months, 30 gr. daily with onset of labor the second day.
3. Gravida, 5 months, 100 gr. over a period of 5 days before abortion.
4. Gravida, 7½ months, 280 gr. before premature labor. Child lived.
5. Gravida, 8 months, 300 gr. administered prior to onset of labor. Child lived.
6. Gravida, 6 months. Aborted after 7 to 9 days of tertian fever. Quinine probably had been given at home.
7. Gravida, 4½ months. Negress with quartan malaria. Aborted after 100 gr. of quinine given over a period of 4 days.
8. Gravida, 8 months. Premature delivery. Infant weighed 3 pounds 5 ounces, the mother had severe estivo-autumnal malaria with daily chills and coma. She received 20 to 30 gr. of quinine prior to delivery.

The following lists the 5 patients who aborted or had labor associated with an attack of malaria, but before quinine was administered:

1. White woman, aged 20 years, at term, estivo-autumnal malaria, comatose, died following delivery of stillborn infant.
2. Gravida, 6½ months, stillborn, labor before quinine given.
3. Gravida, 2 months, began to abort prior to administration of quinine.
4. Gravida, 4 months, aborted before treatment began.
5. Gravida, 8½ months, premature delivery during an attack of estivo-autumnal malaria before quinine was given.

Mortality.—One white woman, 20 years of age, pregnant at 8 months, and stricken with estivo-autumnal malaria, was in coma for two days and died after stillbirth.

The maternal mortality was about 4 per cent and the fetal mortality about 60 per cent.

In the first trimester, 2 patients had attacks of malaria, one tertian and one estivo-autumnal. The former aborted, the fetus dying probably before the administration of quinine. The other patient went to term and delivered a live baby in spite of a very severe prolonged attack (Case 1).

CASE 1.—White woman, aged 18 years, primigravida, became ill with estivo-autumnal malaria at three months' pregnancy and for four months she was recorded to have chills and fever daily. She had headache, dizziness, dyspnea, fainting attacks, and became extremely anemic, the lowest recorded red blood count being 1,090,000, white corpuscle count 7,500, and hemoglobin Dare 10 per cent. She lost weight to 87 pounds. She was treated by repeated transfusions totaling 3,000 c.c. and an aggregate of 350 gr. of quinine. In spite of all of this and two attempts to induce labor by castor oil and strychnine she continued pregnant to term, when she spontaneously gave birth to a healthy live baby weighing 7 pounds 2 ounces.

In the second trimester of pregnancy 7 patients had malaria: 4 tertian, 1 estivo-autumnal, 1 quartan, and 1 not stated as to type. Two aborted during the attack and a third bled vaginally but went home undelivered. One negress with quartan type fever 4½ months pregnant aborted after she had received 100 gr. of quinine over a period of four days. Three patients were pregnant at six months, one miscarried after ten days of illness, and the other two went home undelivered after recovery from the malaria attacks.

In the third trimester there were 18 patients; one at six and one-half months (tertian) aborted; one at seven months not delivered; one at seven and one-half months delivered prematurely; nine were at eight or eight and one-half months' gestation; six of these delivered spontaneously and 3 went home undelivered. Altogether there were 15 at eight months to term. Twelve delivered live babies, the largest 7 pounds 7 ounces and the smallest 3 pounds 5 ounces. The smallest one and probably another of these babies died before the mothers left the hospital. Three women went home undelivered but in good condition and with living fetuses. There was one maternal death after a stillbirth at term.

From this study the rule may be suggested that the danger to the fetus is greater the earlier in pregnancy that the attack occurs, but that the danger to the mother is greater if the attack is late.

ROLE OF THE PLACENTA IN MALARIA

A few studies in the more recent cases of malaria were made in regard to the placenta. These are few because delivery rather seldom took place during an actual crisis and often after the blood stream had been pretty well cleared of parasites. In those few cases (4), in which we were able to obtain the placenta at the height of the attack, the maternal red cells were loaded with parasites. Possibly on account of the relative stagnation of the maternal blood in the placental sinuses the placenta becomes a veritable storehouse similar to the spleen, and abortion or premature labor may be a protective measure. In no case have we* been able to establish the idea of transmission to the fetus by finding parasites in the fetal circulation of the placenta. Apparently from this study the cause of abortion or premature labor seems to be in the malarial attack itself more than in the therapy used, although quinine has the reputation of having oxytocic principles. Answer to the inquiry of just how the onset of labor is induced by malaria is not forthcoming. In every case where labor is brought on in association with a malarial attack, observation should be recorded as to whether uterine contractions occur first or vaginal bleeding is first, this with an effort to find out whether the fault lies in the uterine muscle or in the placental attachment. In every case in this series in which that was recorded, vaginal bleeding was first, and in one or two cases the patient recovered from this without aborting. Consequently, it is suggested that the lesions lie in the placental attachment, and that small retroplacental hemorrhages take place followed by uterine contractions and labor in those women who abort or have a premature labor.

SUMMARY

1. Malaria complicated pregnancy in this locality during a period of twenty years, once in 727 live white births and once in 2,260 negro livebirths recorded.

*In cooperation with Dr. V. P. Sydenstricker.

2. With the youngest patient 15 and the oldest 41, three-fourths were under 26 years of age. Two-thirds were in the last trimester of pregnancy. It was more frequent in white women.

3. The symptoms were mainly those of recurrent high fever and anemia. Most were treated with quinine, and its effect in regard to pregnancy was studied.

4. The maternal mortality was about 4 per cent; fetal approximately 60 per cent. It seems that an attack of malaria is more fatal to the fetus if occurring early in pregnancy and more dangerous to the mother if occurring late.

5. The maternal blood of the placenta apparently becomes a storehouse for the malarial parasites, but in no case could we find them in the fetal blood.

PREGNANCY IN UTERUS DIDELPHYS*

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A BRIEF survey of the literature of developmental abnormalities of the uterus and its appendages leaves one with the impression that there is some confusion in the use of terms to describe the anomaly herewith presented. For that reason, it may be well to state at the outset that the term "uterus didelphys" is used as defined in Dorland's American Illustrated Medical Dictionary: "either of two distinct uteri occurring side by side in the same individual." In addition to this duplication of the entire uterus, the patient who is the subject of this report exhibited also a septate vagina with no demonstrable communication between the two canals.

At first thought one might consider this complete duplication of the birth canal an extremely rare occurrence. However, even an incomplete search of the literature of the past ten years discloses eleven such cases and the fact that at least four of these were not suspected until found at laparotomy or at autopsy necessitates the conclusion that the condition is present not too infrequently.

B. H., 22 years old, white, a primipara, applied for prenatal care in the Out-Patient Clinic of Firmin Desloge Hospital of St. Louis University on June 14, 1939. Past history was generally negative; there had been no operations. Family history was not significant. She had been married for two and one-half years with no previous pregnancy, and her husband was said to be in good health. The menstrual flow appeared at the age of 12, the menstrual periods had been regular every twenty-eight days, lasting seven days, and the flow was described as profuse. There had been severe abdominal cramps on the first day of each period. The last menstrual period had occurred two months previously on April 18, 1939. Physical examination disclosed the following: Weight, 127 pounds; blood pressure 95/60; pulse, 84 per minute; temperature, 98.6° F. Tenderness was noted in both lower quadrants, and bilateral, firm masses were described on either side of the midline just above the symphysis. Vaginal examination revealed the presence of a septate vagina and a severe vaginitis which made complete examination impossible. For this reason it could not be determined whether a double cervix was present or not. *Trichomonas vaginalis* was found in the discharge from the vagina. Pelvic measurements were as follows: spines, 25 cm.; crests, 31 cm.; E. C., 18 cm. bi-tuberous, 9 cm. Internal measurements could not be made because of the painful vaginitis. Treatment of the trichomonas infestation was instituted and a diagnosis of pregnancy in a uterus didelphys was recorded upon pelvic examination at a subsequent visit to the clinic. There are many instances recorded in the literature of women with double uterus who have been delivered without incident via the normal passages, and it was felt that this patient might well be given a trial labor, should she

*Presented at a meeting of the St. Louis Gynecological Society, December 12, 1940.

carry her child to term. It was anticipated that removal of the vaginal septum at the time of delivery would probably be necessary, and it was hoped that the nonpregnant uterus might not interfere too seriously with the mechanism of normal labor.

The patient was seen at regular intervals in the clinic, and except for a greater than average gain in weight (45 pounds) and recurrence on several occasions of the vaginitis previously noted, the pregnancy progressed normally until admission to the hospital at term on Feb. 7, 1940.

On admission, the patient was having contractions at intervals of five to six minutes, lasting thirty to forty seconds and was losing a moderate amount of amniotic fluid, the membranes having ruptured two hours previously. The McDonald measurement was 32 cm. and the fetus lay obliquely in the abdomen with the breech in the left iliac fossa and the head in the right upper quadrant. The fetal heart tones were regular and strong. On rectal examination the presenting part could not be determined; it was thought that the cervix lay in the left vaginal fornix and was dilated approximately 4 cm.

A flat plate of the abdomen revealed an apparently full-term pregnancy with the fetus presenting by the breech. X-ray pelvimetry by the method of Thoms gave the following diameters: Transverse diameter of inlet, 14.5 cm.; anteroposterior diameter of inlet, 10 cm. Laboratory examinations of urine and blood revealed nothing of significance.

During the twelve hours after admission the patient continued in active labor. Contractions occurred every two to three minutes and were moderately strong. One and one-half grains of seconal was given shortly after admission, and the same drug in a dose of 4.5 gr. was given about six hours later with only fair relief of pain. Vaginal instillation of a 1-1000 aqueous solution of zephiran (high molecular alkyl-dimethyl-benzyl ammonium chloride) was carried out every four hours, and the patient received an intravenous infusion of 500 c.c. of 10 per cent glucose in normal salt solution.

There was no evident progress of the labor and the fetal heart tones had gradually become more rapid, reaching a rate of 190 per minute. The patient's temperature had risen to 102.8° F. and examination of the nose and throat and of the chest disclosed nothing significant. Urinalysis remained entirely negative.

At this time a vaginal examination was made in order to determine the precise stage of labor and to discover, if possible, the cause of the dystocia. It was found that a larger vagina on the patient's left side and admitting two fingers easily was separated from a smaller vagina on the right side by a septum which extended from the vault to a point just inside the introitus. Two distinct, though somewhat poorly developed cervices were found and two uteri could be made out. The pregnancy appeared to be in the right uterus while the left uterus, which was quite soft and approximately the size of a twelve to fourteen weeks' gestation, was empty. The left cervix admitted one finger and the right (pregnant) cervix barely a finger tip.

Lipiodol (15 c.c.) was introduced by means of a catheter into the left uterine cavity and an x-ray film was made. The report reads in part, "—apparently a bicornuate uterus, the pregnancy being in the right portion of the uterus." It might be added that no communication between the cavities is demonstrable (Fig. 1).

Cesarean section was advised because of the evident fetal distress (rapid heart) and because of the obstacle to engagement offered by the nonpregnant, left uterus and the probable rudimentary nature of the cervix and possibly of the uterine muscle.

A low cervical section was performed, using the double flap (Beck) technique. Anesthesia was gas-ether. The right uterus contained a full-term fetus. The uterus was markedly elongated, the musculature was poorly developed, and about 0.5 cm. in thickness. At the right side of this uterus were attached the round and broad ligaments, a tube in the normal position, and a normal ovary. The left uterus was about 5 by 7 by 9 cm., and at its left border it displayed the normal attachments. The left ovary contained several follicular cysts. The adjacent medial borders of the two uteri were devoid of attachment above the level of the vaginal vault.

After mobilizing an upper and lower peritoneal flap, the uterus was incised longitudinally in the lower uterine segment. A living, female infant was extracted by the breech. The placenta was attached in the posterior portion of the fundus and

was removed. The uterus did not contract well despite the injection of oxytocics, and there was troublesome bleeding from the needle puncture sites during the closure of the incision in which three layers of No. 2 20-day chromic catgut were placed and in addition several mattress sutures for hemostasis. The previously mobilized peritoneal flaps were overlapped and the abdomen closed in the usual manner without drainage. Two ounces of zephiran (high molecular alkyl-dimethyl-benzyl-ammonium chlorides in aqueous solution 1-2000) were poured into the peritoneal cavity before closure.

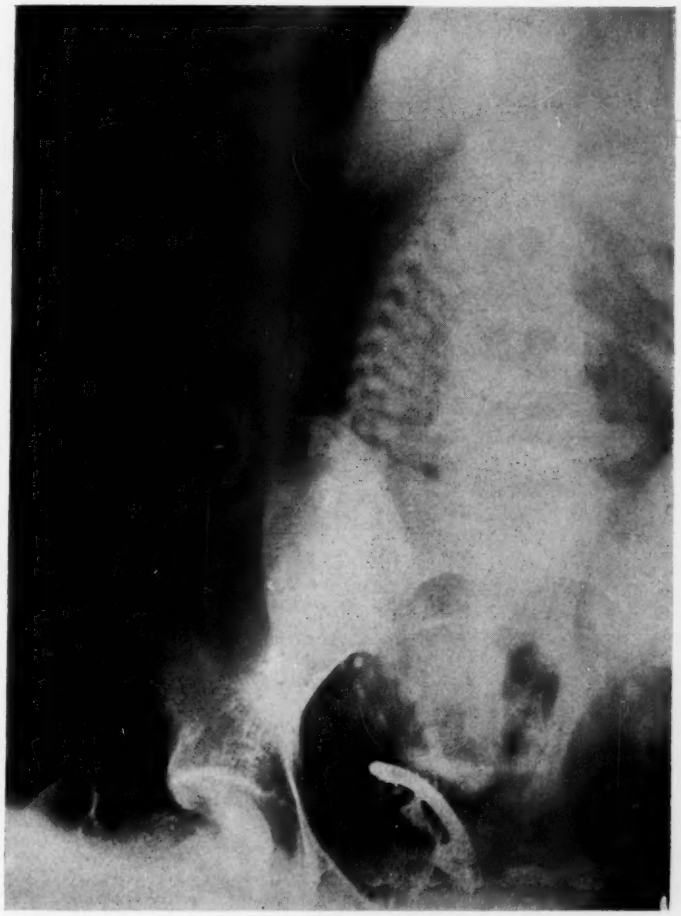

Fig. 1.—Fetus presents by the breech. Lipiodol has been injected into the nonpregnant uterus.

The immediate postoperative condition of the patient was fair (blood pressure, 110/80, temperature, 98.8° F., pulse, 180, good volume). She received a transfusion of 1,000 c.c. of banked blood (equivalent to 400 c.c. of whole blood) during closure of the operative wound.

The postoperative course was stormy during the first ten days. The temperature ranged from 100 to 102° F. except for a posttransfusional rise of 104.5 F. on the sixth day. The pulse remained rapid but of good quality. On the tenth postoperative day the temperature returned to normal and remained so thereafter.

The leucocyte count was never increased above the 8,700 recorded on the first postoperative day, and on the ninth day was 8,300 with a very slight shift to the left in the differential count. The red cells on the ninth day were 3,870,000 and the hemoglobin 11.3 gm.

Administration of neoprontosil was begun immediately following operation, and after the second day, the patient received 60 gr. per twenty-four hours until the drug was discontinued on the eleventh day.

Transfusions of 1,000 c.c. of banked blood were given on the fifth and seventh postoperative days, the latter being followed by a severe febrile reaction. No urinary symptoms were noted.

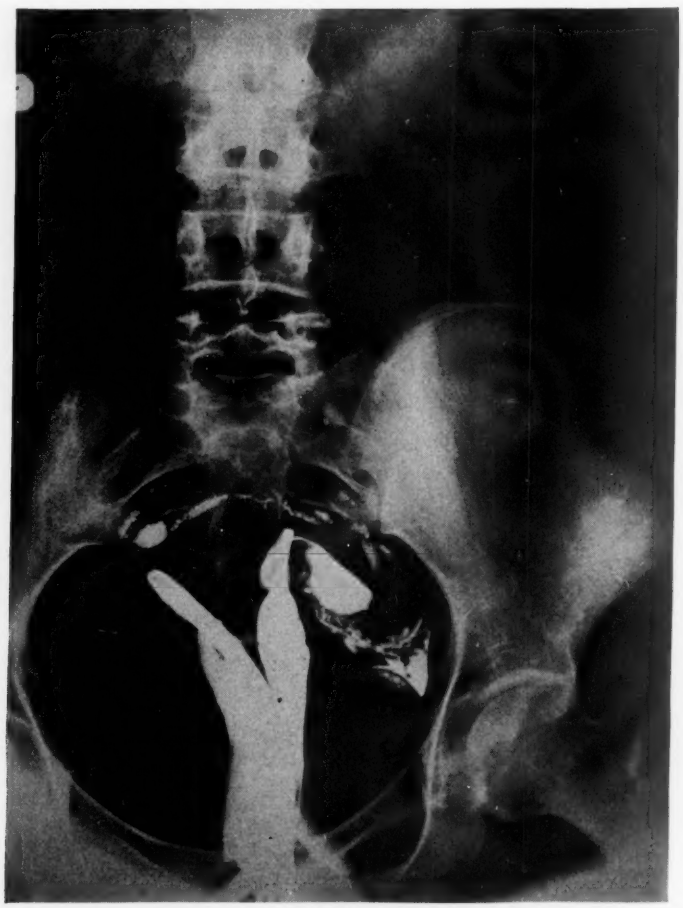

Fig. 2.—Eight months post partum. Two distinct uterine cavities are visualized. Right tube not well outlined.

A small superficial wound abscess was evacuated on the sixth day, and all sutures were removed on the twelfth day. Involution of the right (pregnant) uterus was delayed, and on the twelfth day the fundus was 4 cm. below the umbilicus and slightly tender. It was impossible during the puerperium to follow the involution of the left uterus. It was noted that the lochia rubra was of a brighter than usual color and the amount was definitely more profuse than customary.

At the time of discharge from the hospital on the thirtieth postoperative day, mother and child were in good condition.

The patient was seen in the out-patient clinic on March 25, 1940, six weeks after delivery, and at that time the abdominal wound was completely healed, clean, and dry. Vaginal examination was impossible because of severe vaginitis and the accompanying discharge was positive for *Trichomonas vaginalis*. During the following four months I did not see the patient, though she continued to report to the

clinic for treatment of her vaginitis which showed, however, no improvement following the use of various antiparasitic preparations and the prescription of an acid douche. It is interesting to note that this failure of treatment was apparently due to a failure to recognize the necessity for proceeding against the invading parasite in both vaginas. The various interns who saw the patient had made a strenuous effort to eradicate the infestation in the larger (left) vagina but had neglected the smaller right cavity which acted as a reservoir. After explaining to the patient the technical difficulty involved and teaching her to insert a suppository and later the douche tip in each side following careful insufflation of each vagina, the vaginitis cleared up and with it the discharge. Neither has recurred up to the present time.

On Oct. 10, 1940, the patient was readmitted to the hospital for further study. Under morphine and hyoscine analgesia a pelvic examination was made. The vaginal mucosa was normal in appearance; there was no discharge and no vaginitis. Bimanual examination disclosed the right vagina to be narrow but deep, admitting one finger. The right cervix was about 2 cm. in length, moderately firm and the external os closed. The right uterus could be palpated and was carrot-shaped, freely movable and apparently about 7 cm. in length. The left vagina admitted two fingers easily; the cervix was extremely short, being only a button-like protrusion in the vaginal vault. The left uterus could not be definitely outlined.

A Ferguson speculum was introduced into the right vagina and a soft rubber catheter (No. 18), threaded onto a stylet, was passed into the right uterine cavity. The Ferguson speculum was then removed and a bivalve speculum placed in the left vagina, and an olive-tipped metal cannula was introduced into the left uterine cavity. A total of 12 c.c. of an opaque medium was then injected into each cavity and an x-ray film was exposed. The roentgenologist's report reads in part as follows, "—opaque medium is visualized in the peritoneal cavity. There seems to be some dilatation of the left tube. The right tube is not well vizualized." To this may be added the remark that the complete duplication of the uterus with entire absence of communication between the two cavities is well demonstrated. The reason for failure to visualize the right tube, of course, lies in the technical difficulty involved in injecting both uteri simultaneously. The size of the right vagina and the close proximity of the two cervices would not permit the passage of two metal cannulas equipped with olive tips, and some of the injected medium had escaped from the right uterus alongside the soft catheter (Fig. 2).

SUMMARY

A case of uterus didelphys with complete septate vagina is reported in which pregnancy occurring in one uterus was terminated by cesarean section because of dystocia. The dystocia was brought about by inability to dislodge the nonpregnant uterus which blocked the inlet to the pelvis.

Pregnancy may have occurred as a result of internal migration of the spermatozoa. This presumption is based on the fact that pregnancy occurred in the right uterus while coitus was obviously possible only in the left vagina, there being no demonstrable communication between the two vaginas. It is, of course, possible that external migration of the sperm from the left to the right vagina may have occurred.

Vaginitis, resulting from trichomonas infestation, was a complicating factor during the postoperative period. It was very resistant to treatment until measures were taken to insure that not only the insufflation carried out in the clinic but the patient's self-treatment at home was directed simultaneously to both vaginal cavities.

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INTESTINAL OBSTRUCTION COMPLICATING PREGNANCY*

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FIVE cases of intestinal obstruction complicating pregnancy have been seen at the Magee Hospital in 45,000 deliveries during the past twenty years. As they differ in many respects, these cases serve to emphasize that such complications are individual problems, requiring separate and distinct surgical and obstetric considerations in the management of each.

Case 1.—Mrs. K. B., aged 21 years, para ii, six and one-half months pregnant, was admitted to hospital Dec. 25, 1930. Eight weeks previously this patient had undergone an appendectomy, at which time a mildly inflamed appendix kinked by numerous adhesions had been removed through a small McBurney's incision. A postoperative course of sixteen days was uncomplicated, and until three days prior to admission she had been free from abdominal pain.

At the time of admission the patient was seriously ill. She had been suffering with severe pain in the right side of her abdomen for three days. During that time she had vomited almost continuously and had not had a bowel movement for two days.

On examination the patient was very toxic and definitely dehydrated. The abdomen was distended and tympanitic, with spasticity and extreme tenderness over the entire right side. Temperature was 101° F.; pulse, 136; leucocyte count, 28,500. A diagnosis of acute intestinal obstruction was made, and the patient was prepared for immediate operation. Under spinal anesthesia a midline incision above and below the umbilicus was made. The abdominal cavity contained 500 c.c. of turbid fluid. Two thick bands of adhesions were found at the base of a loop of terminal ileum, and at this point the enclosed intestine was tightly constricted. This entire loop, which measured 12 cm. in length, was gangrenous. The fibrous bands were divided, and 18 cm. of ileum were resected. A side-to-side anastomosis was performed and drainage was secured through a stab wound in the right flank. The midline incision was closed. Several times during the operation the patient vomited fecal fluid.

Following operation the temperature rose rapidly to 106° F.; pulse was 160. The abdomen presented signs of generalized peritonitis. Supportive measures were employed, but the patient died twenty-four hours after operation. An autopsy was not performed.

Delay in surgical intervention is unquestionably the greatest factor contributing to this unfortunate outcome. In this respect, this patient's history is typical of many of the mortalities reported. Quite often this factor is not within the power of the surgeon to correct, and this suggests the need for earlier hospitalization of gravid patients presenting any part of the symptom complex of partial intestinal occlusion, particularly in the presence of an abdominal scar.

Case 2.—This is a report of intestinal obstruction in pregnancy, due to volvulus.

According to Kornfield and Daichman only one case of volvulus complicating pregnancy had been reported in the United States up to 1934. A rather careful search of the literature showed no additional such instance to date. This second case seems somewhat unusual in this respect.

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Mrs. A. S., aged 24 years, gravida i, was admitted April 5, 1929. She was four months pregnant. Her chief complaints were nausea, continuous vomiting, and intense abdominal pain. Seven years previously a right inguinal herniotomy and appendectomy had been performed through a single incision. In the past two years she had been troubled with constipation. Since the onset of pregnancy this symptom had become more severe, and she began having periods of nausea and vomiting associated with attacks of abdominal pain.

All these symptoms increased in severity in the two weeks prior to admission, and on arrival at the hospital, she was suffering with intense pain, localized to the right lower quadrant. There was marked abdominal distention and tympany. The lower right side was exquisitely tender. Temperature, pulse, and respirations were not elevated. Immediate operation was advised.

Under spinal anesthesia the abdomen was opened by a right rectus incision. The abdominal cavity contained 300 c.c. of thin serosanguineous fluid. The terminal ileum was enormously distended. One darkly discolored loop of bowel, measuring 20 cm. in length, was twisted upon itself at a point 2.5 cm. from the ileocecal valve. This twist was easily corrected, inasmuch as there were no constricting nor adjoining adhesions. Immediately, the gas in the obstructed portion of the bowel was liberated, with improvement in the color and appearance of the terminal ileum and its mesentery. The uterus, enlarged 6 cm. above the symphysis, showed no abnormalities. The abdomen was closed without drainage.

Following operation the abdominal distention subsided. After the fourth day the patient was having normal bowel movements. She was discharged on the twenty-fifth day. Except for occasional periods of nausea and vomiting, she remained well throughout the remainder of her pregnancy, and was delivered by midforceps of a normal infant at term. This patient's subsequent history showed that she remained free from symptoms suggestive of recurrence of intestinal obstruction. A second pregnancy was uneventful throughout.

A supravaginal hysterectomy was performed eleven years later because of profuse metrorrhagia. It was interesting to observe that there were no adhesions involving the intestinal tract, although a pale firm area of scarring about the ileum at the site of the previous volvulus was seen.

Undoubtedly the time of operation was a very important element in this patient's successful recovery. It is reasonable to assume that further delay may have permitted irreversible damage to the twisted loop of bowel, altering definitely her postoperative course.

CASE 3.—The following is a report of partial intestinal obstruction occurring in pregnancy, which, with careful observation, was amenable to conservative management:

Mrs. C. D., aged 26 years, gravida v, was admitted July 26, 1938. She was six and one-half months pregnant and complained of severe cramplike abdominal pains, nausea, and vomiting. Her past medical history showed that in addition to two abortions she had had two classical cesarean sections, one in 1934 and the second in 1935. Each section had been indicated because of a cephalopelvic disproportion, and at each operation the abdomen had been entered through a left rectus incision. There was no history of sepsis following the termination of each of these four pregnancies, and the period of convalescence had in each instance been uncomplicated.

To this patient the appearance of abdominal pain, nausea, and vomiting of such severity in the latter months of pregnancy was an entirely new and unprecedented occurrence. Shortly after admission the abdominal pain became localized to the left side. Examination at this time disclosed a moderately distended abdomen. There was marked tenderness over the left lower quadrant and the abdominal muscles were tense. Peristalsis was not prominent but there was an occasional loud gurgle suggestive of fluid in the presence of trapped gas. The uterus was relaxed and the fetal heart rate was 140. The temperature was 100; pulse, 104; white blood count, 7,400 with 76 per cent polymorphonuclears; 24 per cent lymphocytes; CO_2 combining

power, 34.3 per cent; chlorides, 453, mg.; urea, 10.3 mg.; urinalyses, negative. With the administration of morphine and hot abdominal stupes, the paroxysmal character of the abdominal pain subsided and the vomiting ceased after six hours. While it was felt that this patient probably had a partial intestinal obstruction due to postoperative adhesions, the appearance of such improvement seemed to warrant a conservative form of management, along with constant and careful observation. Accordingly, the sedation and hot abdominal stupes were continued and the patient was given daily high colonic irrigations. Clear liquids were given by mouth on the second day. Improvement continued and she was discharged after four days. A nonresidue diet was prescribed, and she was seen weekly throughout the remainder of her pregnancy. On several visits attacks of abdominal "cramps" were described, each of which had been relieved by enemas.

On Sept. 18, 1938, this patient was readmitted and a third classical cesarean section was performed. The Fallopian tubes were ligated, and several intra-abdominal adhesions involving the uterus, omentum, and small intestine were divided. The patient had an afebrile and uncomplicated puerperium. After returning to normal life, she continued to have occasional attacks of abdominal pain which, however, were relieved within a few hours after taking an enema. Recently these attacks have become much less frequent and much less severe, due in part at least to a more careful and intelligent management on the part of the patient.

CASE 4.—Mrs. A. F., aged 26 years, gravida ii, eight and one-half months pregnant, was admitted to the hospital Feb. 3, 1940. She complained of severe pain in the right side, vomiting, and marked weakness.

Her pregnancy had been uneventful until 5:00 A.M. on the day of admission, when she was awakened by a sharp pain in the right lower quadrant, referred to the midlumbar region. Vomiting followed in two hours, and was repeated five times prior to admission. In 1925 she had had an exploratory laparotomy because of abdominal pain associated with the history of having swallowed a fishbone. Her appendix was removed at that time, and she had not complained of any abdominal symptoms until the onset of the present illness. Her first pregnancy in 1938 was uncomplicated, and terminated in the spontaneous delivery of a normal child.

Examination showed a moderately obese white female lying in bed, moaning and rolling from side to side. She complained of a constant stabbing pain in the right lower quadrant and held her right leg flexed upon her abdomen. Her skin was pale and moist. Temperature was 97° F. and pulse 100. The abdomen was moderately distended, and there was an old irregular right rectus scar, extending from the iliac spine to the costal margin. Marked tenderness was present below the angle of the incision. Peristalsis was present on the left side and absent on the right. The uterus showed no evidence of irritability. The presenting part was not engaged. Fetal heart sounds were 140. The cervix was not dilated nor effaced. The leucocyte count was 12,300; polymorphonuclears, 90 per cent; lymphocytes, 10 per cent; red blood count, 3,440,000; Hb., 58 per cent. Chlorides were 363 mg.

It was felt that this patient had developed a mechanical intestinal obstruction due to adhesions at the site of previous laparotomy, and with evidence of impending shock, cesarean section with prompt release of the obstruction was indicated. A classical cesarean section was performed, using gas-local anesthesia, and a living child was obtained. Exploration of the right side of the abdomen, following closure of the uterus, revealed numerous fibrous bands and adhesions which, along with pressure from the enlarged pregnant uterus, had caused marked distortion of the contour of the ascending colon and cecum. At one point in the ascending colon a moderate-sized fecal impaction was broken up. Then various adhesions and fibrous bands were individually clamped, cut, and ligated. Immediately following operation the patient was given 500 c.c. of citrated blood, and was placed on the Ochsner peritonitis regime. Within the first twenty-four hours postoperatively, she developed a marked paralytic ileus, which was managed successfully by Wangensteen drainage. There was a septic febrile reaction, with the temperature reaching 103° F. and pulse 124, on the third day. This fell steadily to normal levels by the sixth day.

Enemas were effectual, with return to normal evacuation on the eighth day. The remaining postoperative course was uneventful.

The *fifth case* is interesting in that at operation an old appendiceal abscess was encountered, which had not been suspected, although the patient had been under observation for several weeks.

Mrs. C. H., a colored female, aged 35 years, gravida vi, seven and one-half months pregnant, was admitted to the hospital July 17, 1940. She was suffering with intermittent attacks of midabdominal pain, which she insisted on associating with a bad fall four weeks previously. At a local hospital the abdominal pains, at that time, and on subsequent visits were dismissed as being due to pressure from the enlarged pregnant uterus. The abdominal pains continued and she began to vomit. Distention and obstipation followed. At the time of admission she had passed no formed stool for two weeks. Recently she had had diarrhea with passage of considerable flatus.

Her past medical history disclosed that she had been given two courses of antisyphilitic therapy. There had been one miscarriage and four full-term pregnancies, all terminating normally.

On examination the abdomen was markedly distended and tympanitic. Peristalsis was quiet except for an occasional rush, which was then associated with pain, and definite tenderness, localized to the midline just above the umbilicus. The uterus was not contracting. The fetal heart sounds were 144. The initial laboratory work showed red blood count, 3,160,000; Hb., 63 per cent; white blood count, 7,500; polymorphonuclears, 63 per cent; lymphocytes, 37 per cent; nonprotein nitrogen, 27.5 mg.; sugar, 71 mg.; chlorides, 462 mg.; sedimentation time, 10 minutes, CO_2 combining power, 45.7 per cent; serology, negative; urinalyses, negative. It was felt that this patient had a partial intestinal obstruction, mechanical in type, with the etiology obscure.

She was given morphine at regular intervals, 2,000 c.c. of 5 per cent glucose in normal saline by vein daily, frequently repeated tidal wave enemas, hot abdominal stupes, and nothing by mouth. Within forty-eight hours definite improvement was noted. The distention became less and the vomiting ceased. After four days she was passing large quantities of liquid stool and was given a soft nonresidue diet.

Two weeks after admission a gastrointestinal series showed a partial bowel obstruction in the midileum, probably due to adhesions. Repeated blood counts showed no evidence of leucocytosis. There had been no elevation of temperature or pulse.

Twenty-nine days after admission the patient's membranes ruptured spontaneously, and after an hour and sixteen minutes of fairly hard contractions, she was delivered spontaneously of a normal four and one-half pound living infant. An afebrile post-partum course ensued.

On the twelfth post-partum day, a severe pain appeared in her right lower quadrant, followed by a steadily increasing abdominal distention, as well as a rather marked nausea and a mild degree of shock. There was marked tenderness in the right lower quadrant. As these signs and symptoms persisted with increasing severity, laparotomy was advised.

On opening the abdominal cavity, an old appendiceal abscess was encountered, extending from the cecum along the right side of the pelvic cavity to the cul-de-sac. One fecalith was found. There were adhesions of small bowel to the abscess, and in several places the small bowel was sharply angulated, forming a partial obstruction. The right Fallopian tube was enlarged and adherent to the mass. The appendix was not located. The adhesions were separated to relieve the obstruction, and the right Fallopian tube was removed. Three drains were placed in the abdomen before closure.

The patient was placed on peritonitis regime. She maintained a temperature near 101° F. with a pulse of 100 until the ninth day when the temperature and pulse returned to normal following removal of the drains. After the sixth postoperative day, she retained a soft diet and had normal bowel movements. She was discharged from the hospital Sept. 22, 1940, after sixty-seven days of hospitalization. Her condition was very good.

In retrospect, this patient's first attacks of pain were probably due to an attack of acute appendicitis which went on to rupture and abscess formation. Fortunately, the patient was able to wall off this infection satisfactorily, and even further to acquire a degree of immunity to organisms within the abscess. The absence of fever and leucocytosis were probably important reasons for not suspecting an infectious process.

This case also illustrates that conservative management of partial intestinal occlusion may be employed to excellent advantage. It serves to show, however, that constant observation, preferably with hospitalization, is extremely important if the patient is to receive the benefit of prompt surgical intervention when it is indicated.

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CALCIFIED FIBROMYOMAS

Report of 4 Cases

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SINCE the reports of Peacock[1] and Wang,[2] there has been no mention of calcified fibromyomas in the available literature. During the last eight months (January to October, 1940) we have encountered 4 cases presenting calcification occurring in fibromyomas. During this period of time 23 hysterectomies were performed in which fibromyomas were the operative indication in 20, carcinoma of fundus in 1, and diffuse endometrial polyps in the other 2 cases.

A consideration of the 4 cases showing calcified fibromyomas is in order, and the case reports are herewith given:

Case 1.—M. F., colored, female, widow, aged 52 years, gravida 0, was admitted to the hospital with the chief complaint of abdominal pain. Pain began twenty-four hours before admission without prodromal symptoms. The onset was sudden, forcing the patient to lie down because of a "faint feeling." This was followed by a chill, abdominal enlargement, with exquisite abdominal tenderness, nausea, and vomiting following intake of food or fluid. In the past history the patient was seen at the age of 48 years with fibromyomas of the uterus, causing pain in the right flank; surgical intervention was refused at that time. Physical examination on this admission revealed an obese negro female with a temperature of 99.2° F., pulse 76, respirations 20, and blood pressure 194/100. The heart was enlarged, with the left border dullness being 2 cm. to the left of the midclavicular line, and there was a soft systolic murmur over the apex.

The abdomen was obese and there was exquisite tenderness with rebound phenomenon throughout. There was a hard tumor mass palpable in the left hypochondrium which was not movable. Pelvic examination revealed the pelvis filled with a hard nodular tumor mass. The white blood count was 14,300 with 6 stabs, 80 neutrophiles, 8 monocytes, and 6 lymphocytes. Sedimentation time was 46 and 80 mm. for the first and second hours, respectively. At operation a large, extremely firm mass, measuring 18 cm. in diameter, was found lying in the left mid-abdomen, and when delivered was attached by a pedicle 10 cm. in length to the uterus at the

right broad ligament. The pedicle was twisted and had caused some torsion of the uterine fundus, and the uterus and fundus were surrounded by omentum. The adnexa were normal to gross examination. Because of the patient's hypertension, a subtotal hysterectomy was deemed inadvisable and the tumor with the pedicle was removed. Patient was discharged fifteen days later, following an uneventful postoperative course.

Pathologic Description.—Gross: Specimen consisted of a mass of hemorrhagic, irregular, nodular, stony-hard tissue, measuring 19 cm. in diameter. There was a mesenteric adhesion and a twisted 2 cm. pedicle attached. On sawing through the mass, it was composed of dense, hemorrhagic fibrous tissue with calcium deposits scattered throughout. Prior to sectioning, x-rays were taken showing a diffuse calcification. *Microscopic:* Sections consisted of hyalinized fibrous tissue, containing large amounts of calcium deposited throughout. Scanty traces of muscle tissue were seen, and there was marked extravasation of blood in some areas. The vascular supply was interesting in that the vessels were surrounded by calcium deposits frequently. The vessels were, however, patent, being gorged with erythrocytes now. In areas capillary rupture was seen accounting for the hemorrhage visible grossly. There was no histologic evidence of malignancy or organized bone formation. *Diagnosis:* Uterine fibromyoma, pedunculated, calcified, twisted.

Case 2.—E. J., colored, female, aged 52 years, gravida ii, para ii, was admitted with pain in the lower right quadrant of the abdomen. It was accompanied by nausea and vomiting on two occasions. Pain was described as being severe, intermittent, and there was residual tenderness in the lower right quadrant and right flank. There were no urinary symptoms. *Past medical history:* Twelve years prior to admission the patient was seen in this clinic at which time she had acute pelvic inflammatory disease with a 3-plus Wassermann reaction. Menses ceased six years ago without difficulty. Physical examination revealed temperature 99.0° F., pulse 88, respirations 16, and blood pressure 150/90. Examination was essentially negative, with the exception of the abdomen which was protuberant, particularly in the lower portion. There was marked tenderness in the lower right quadrant and over the right flank. There was no tenderness in either costovertebral angle. Rebound tenderness was referred to the lower right quadrant; there was no muscle rigidity. Pelvic examination showed a lacerated, eroded cervix. The fundus of the uterus could not be definitely outlined although no masses were palpable. Motion of the cervix caused no pain. Urinalysis was essentially negative. White blood count was 11,600 with 9 stabs, 50 neutrophiles, 35 lymphocytes, 5 monocytes, and 1 basophile. Sedimentation rate was 17 and 40 mm. for the first and second hours, respectively. Kahn was 3-2-2. Patient was operated upon three hours after admission, and the appendix, when delivered, showed no gross abnormality. Limited exploration was carried out through the incision, and a pedunculated, subserous, uterine fibroma the size of a golf ball was found on the right side which was removed. Patient was discharged eight days later following an uneventful convalescence.

Pathologic Description.—Gross: Specimen consisted of a round mass of fibrous and muscle tissue, measuring 3.5 by 3 cm. It showed at one point a break in the continuity of the serosal covering which resembled the point of amputation. To palpation it was generally doughy, resilient, and palpable within its substance were numerous, hard calcified areas. On sectioning, the cut surface was arranged in whorls and bundles whose centers were chalky yellow and hard, gritty to palpation. There were no areas of hemorrhage or liquefaction seen grossly. *Microscopic:* Sections consisted of muscle and fibrous tissue arranged in bands and bundles cut in varying planes. The vascular supply to this structure was rather small and the vessels showed intimal proliferation and occlusion in areas. There were large areas of fibrous tissue, containing lacunaelike structures around which were seen deposits of calcium. These represented viable fibroblast nuclei whose cytoplasm had for the most part undergone collagenous and hyaline changes with calcium deposition occurring there. In the sections studied there was no histologic evidence of malignant degeneration. Diagnosis: Subserous, pedunculated fibromyoma, calcification.

CASE 3.—S. W., a colored female, 35 years of age, gravida iii, para i, was admitted to the hospital because of menorrhagia and metrorrhagia, lower abdominal pain, and backache. These symptoms have been present intermittently the last two years. Past history reveals that two years before patient had a hard palpable uterine tumor reaching to the umbilicus, causing pain and tenderness in both adnexa on palpation. Examination on this admission revealed a well-nourished, colored female, whose only positive findings were in the abdomen. Here a nodular, firm mass was palpable, reaching midway between the umbilicus and xiphoid process. There were no other palpable masses. Pelvic examination revealed the cervix displaced forward and the uterus involved in the large abdominal mass described above. This mass was wedged into the pelvis but was movable. The adnexa were not palpable. Urinalysis was within normal limits. Hematologic survey revealed a hemoglobin of 7 Gm. and 2,500,000 erythrocytes. Sedimentation rate was 26 and 56 mm. for the first and second hours, respectively. Kahn was 0-0-0. Following transfusions a supracervical panhysterectomy was performed, bilateral salpingo-oophoritis being present. The postoperative course was somewhat stormy, with the patient developing right bronchopneumonia on the fifth postoperative day. She was discharged from the hospital twenty days postoperatively.

Pathologic Description.—Gross: Specimen consisted of a markedly enlarged, deformed uterus with both tubes and ovaries attached. The uterus roughly covered an area of 30 cm. in diameter and was so twisted and distorted by multiple fibroids that it was impossible to obtain accurate measurements. The fibroids were intramural, submucous, subserosal, and pedunculated. They varied from millet seed to 11 cm. in diameter. On sectioning there were two intramural fibroids which showed deposits of calcium around their peripheries and scattered indiscriminately through the centers. These measured, respectively, 3 and 8 cm. in diameter. The endometrial cavity had lost its normal outline and was encroached upon by numerous fibroids. The lining endometrium showed scattered hemorrhages but no polyps were seen. The Fallopian tubes showed marked stretching, kinking, and distortion by virtue of the growth of fibroids. The ovaries were bound to the tubes by fibrous tissue and showed small cysts beneath the surface. No corpora lutea were seen. *Microscopic:* Sections were composed of large masses of fibrous tissue, running in varying directions and cut on different planes. Scattered throughout were fragments of muscle cells. The areas of fibrous tissue proliferation were encapsulated and at the periphery showed large areas of hyaline degeneration in which there occurred a deposition of calcium material. There was no uniformity of pattern demonstrable in the calcium deposits after thorough study. At first glance it appeared to be deposited in cartilaginous tissue; however, further study showed that the lacunaelike formations were the results of the surrounding hyalinized fibrous tissue, shrinking from the occasionally recognizable fibroblast nuclei. There was no histologic evidence of malignancy seen in the sections studied. Sections of the uterus with endometrium attached showed endometrial hyperplasia with small cyst formation. The endometrium overlying the fibroids showed atrophy with edema and hemorrhages. Sections of Fallopian tubes showed the classical chronic obliterative salpingitis. The ovary showed numerous small follicular cysts and a thick covering membrane. No corpus luteum cysts were seen. *Diagnosis:* Multiple uterine fibromyomas, calcification, chronic salpingitis, chronic oophoritis, follicular cysts, endometrial hyperplasia, endometrial atrophy (pressure).

CASE 4.—H. H., white female, aged 45 years, gravida iv, para iv, was admitted with chief complaint of vaginal bleeding. This bleeding had been present for the past year with periods lasting two to three weeks and causing great weakness. The past history was negative. Patient was married and had four children, the oldest 26 years and the youngest 12 years of age. Examination was essentially negative with the exception of the pelvis. Pelvic examination revealed the uterus enlarged, smooth, and hard, filling the pelvic outlet. The adnexa could not be outlined. The cervix showed bilateral tears. Urinalysis was within normal limits and hemograms revealed 8 Gm. of hemoglobin with 3,670,000 erythrocytes. Sedimenta-

tion rate was 18 and 42 mm., first and second hours, respectively. Serology was 0-0-0. She was given preoperative transfusions of blood, and a supracervical hysterectomy was performed. The adnexa were grossly normal. The postoperative course was uneventful, and the patient was discharged eleven days postoperatively.

Pathologic Description.—Gross: Specimen consisted of uterus, containing a low uterine fibroid. The uterus and fibroid measured 20 by 18 by 10 cm. On sectioning the endometrial cavity was distorted and compressed by the low uterine fibroid, and the lining endometrium was hemorrhagic. There were no polyps seen grossly. Sectioning of the fibroid showed a 1.5 cm. well-circumscribed area of calcification. There was no other gross evidence of retrograde change seen. *Microscopic:* Sections of uterus with endometrium attached were taken through the point where the fibroids were compressing the endometrial cavity and showed marked stretching of the endometrium and narrowing of the layer, the whole being accompanied by edema and scattered, diffuse hemorrhages. The endometrium was atrophic here, although in other areas it was in the late secretory phase, showing occasional scattered basal cyst formations. Sections of fibroids revealed classical bands and bundles of fibrous tissue cut on varying planes. In the area described grossly as being partially calcified, there was seen to be a hyaline degeneration of the collagenous fibrous tissue with deposition of calcium indiscriminately throughout this area. There was no evidence of osteogenesis. *Diagnosis:* Uterine fibroids with calcification, late secretory endometrium, endometrial cysts.

DISCUSSION

The average age of these patients varied from 35 to 46 years. Three of them were negroes; 1, although married, had never been pregnant, the other 3 had had 2, 3, and 4 pregnancies, respectively. One of the patients showed chronic salpingitis and chronic oophoritis with follicular cysts. Two of the patients had normal adnexa, and in the other patient the adnexa could not be explored due to the limited surgical incision. Bleeding and pain were marked symptoms in the 2 patients showing intramural fibroids with calcification. In the 2 cases of pedunculated fibroids, there was no bleeding, and in 1 case (M. F.) there was pain which was probably due to torsion of the uterine body; a case similar in some respects to this one was reported by Roberts.[3] The other patient (E. J.) had unexplained, right-sided pain, which did not recur postoperatively, although no gross lesions were found in the abdomen that could in any way account for the symptoms. The fibromyoma was removed incidental to appendectomy which on gross and histologic examination was normal.

In studying the histology of the fibromyomas from those showing little or no retrograde changes to the one (M. F.) showing almost complete calcification, one is impressed by the sequence of changes as portrayed in sections taken from various lesions. The earliest change is one of proliferation of fibroblast cells between the muscle cells, causing minor compression and atrophy of the muscle cells (Fig. 1). In other areas of the same section one finds almost complete absence of muscle cells and a marked condensation of the fibroblast cells which in areas assume a collagenous aspect (Fig. 2). Careful scrutiny of the vessels in this region reveals no evidence of occlusion or destruction. The next change encountered is one of hyalinization of the collagenous bundles and dense fibrous tissue with the loss of the small interstitial capillaries and venules, this being followed by the deposition of calcium in the intensely hyalinized areas and occurring without any apparent relationship to the larger vessels. The lesions are found immediately surrounding the arteries and also at considerable distances from the visible arteries in the sections. The arterial wall in the majority of instances shows no remarkable medial or intimal changes. The deposition of calcium, once established, could not be seen to be dependent upon any local condition, occurring as it does scattered throughout the hyalinized collagenous tissue, and in places so surrounding viable fibroblast nuclei that at first glance they give the appearance of lacunae formation. In one case (M. F.) the vascular supply must have been adequate up to the onset of the acute

symptoms inasmuch as acute interstitial hemorrhage is seen in the sections, yet no muscle cells and only a few scattered fibroblast cells are seen. By far the greatest portions of the sections are composed of deposits of calcium in an indeterminate supporting stroma. This stroma in the immediate vicinity of the now thrombosed arteries and veins assumes the character of acellular fibrous tissue resembling that

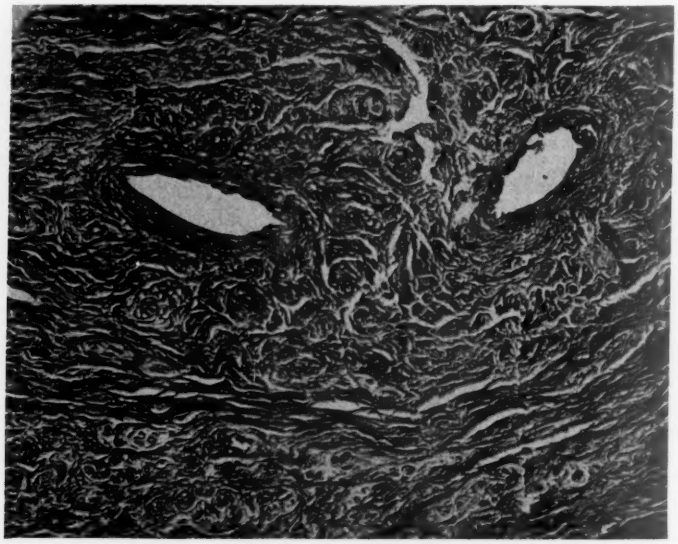

Fig. 1.—Early fibroblast proliferation causing compression and atrophy of the muscle cells. Note the intact vascular supply.

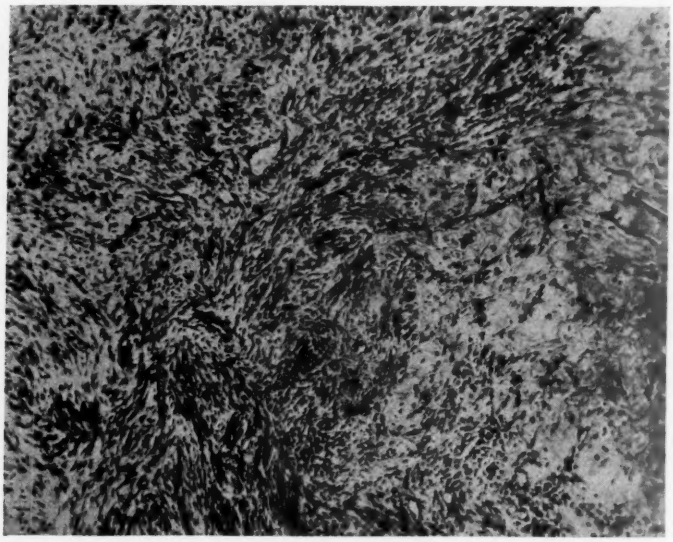

Fig. 2.—Fibroblast cells showing condensation and formation of collagen which in areas shows early hyaline changes.

seen in keloids. This is interesting in view of the finding of 3 of the cases of calcified fibroids occurring in negroes. None of the above cases show external evidence of keloid formation and in our experience here we have encountered only one case of keloid formation occurring in conjunction with fibromyoma of the uterus.

It is seen from the above that no common denominator for the determination of the degenerative changes of calcification can be arrived at in an analysis of the predominating signs and symptoms or in an examination of the pathologic findings of these four cases.

SUMMARY

1. Four cases of calcified fibromyomas are presented. Two cases (pedunculated subserosal) presented signs and symptoms of an acute surgical abdomen. Two cases (intramural) were found in routine pathologic examination and presented the usual symptomatology of fibromyomas.

2. The calcium deposition centers predominantly in areas where collagen has become partially hyalinized regardless of the condition of the vascular supply.

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ANNULAR DETACHMENT OF THE CERVIX

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SPONTANEOUS amputation of the cervix is a rather infrequent complication of labor. The literature reveals only 32 cases, and of these, only 3 are reported in American periodicals. This is a case of spontaneous cervical amputation in which the patient recovered after a prolonged convalescence, and fourteen months later delivered a normal premature infant in the thirty-third week of gestation.

History.—A. C., a colored primipara, 30 years of age, was admitted to Gallinger Hospital on Aug. 24, 1939, after having had an irregular type of labor for about twenty-one hours. She had a hard chill about four hours before admission. Membranes had ruptured seven hours before admission. Last period began on Oct. 6, 1938, making the expected date of confinement July 13, 1939. She had attended prenatal clinic regularly since her sixth month of pregnancy and had received antisyphilitic therapy. She had had a rectal stricture for the past several years which had been dilated on two occasions, and on admission she gave no history of difficulty with bowel action.

Physical Examination.—Temperature was 101.2° F.; pulse, 104; and blood pressure, 130/80. Her skin felt hot and dry. The abdomen revealed a uterus at term undergoing regular firm contractions every fifteen minutes, lasting only a few seconds. The infant was in L.O.T. position with fetal heart sounds in L.L.Q., 164 per minute. The head was well engaged. Marked right costovertebral tenderness was present. Examination of the perineum revealed marked scarring and induration.

Rectal examination revealed a stricture about 4 cm. above the sphincter which had an orifice of about 2 cm. On vaginal examination the vertex was found in L.O.T. position. Cervix was thick and 4 cm. dilated. Diagnoses of lymphopathia venereum with rectal stricture, right pyelitis, and term pregnancy were made.

Laboratory Data.—Blood count revealed Hg 40 per cent (Newcomer): red count, 3,300,000; white count, 20,000. Urinalysis showed 3+ albumin, numerous white blood cells, and a few granular casts. A positive Frei reaction was obtained.

Progress.—Patient was given intravenous glucose and morphine, and an hour after admission she had a hard shaking chill and became quite dyspneic, but improved with further morphine sedation. Eight hours after admission the patient was out of labor and resting fairly comfortably. Fifteen hours after admission her bladder was quite distended and no fetal heart could be heard. Catheterization was impos-

sible until the vertex was dislodged and pressure removed from the urethra by vaginal manipulation. The cervix was now found to be about 7 cm. dilated. A thick anterior lip of cervix was incarcerated between the head and the symphysis. The cervix was forced above the symphysis after displacing the vertex. With this manipulation, a small amount of foul smelling meconium-stained amniotic fluid escaped.

Twenty-four hours after admission contractions were weak and infrequent. Labor was stimulated by minim doses of pitocin. A few hours after the pitocin had been given the patient became quite dyspneic. Respirations were quite deep and 52 per minute. The marked costovertebral tenderness persisted. Intravenous Hartman's solution alternately with glucose was given. Twenty-nine hours after admission she was having strong uterine contractions and the vertex was distending the perineum. While preparing the patient for delivery, contractions stopped again. A vaginal examination revealed vertex in A.P. diameter and no cervix palpable. Pressure on fundus was not sufficient to force vertex over the scarred perineum. A pudendal nerve block was done and forceps were applied. By intermittent tractions the vertex was brought over the perineum without doing an episiotomy through the scarred perineum. The forceps were not removed until after the head was delivered. Following the delivery of the shoulders and with the delivery of the trunk, a small piece of tissue protruded through the vagina.

A foul smelling stillborn male infant weighing 6 pounds 12 ounces was delivered. The placenta was expressed from the vagina twenty minutes later. During the third stage of labor, an estimated blood loss of about 500 c.c. was sustained. The uterus contracted well following administration of intravenous ergometrine. Following delivery of the placenta, a long loop of tissue was seen protruding through the vagina. Examination by palpation revealed it to be attached to the cervix posteriorly, and with the palpation one end came free. Because of the infected field, the attached end was tied off at the base and the remainder cut free. No further bleeding resulted.

The detached cervical tissue was 27 cm. long and 2.5 cm. wide. It had a raw purplish red appearance. The border representing the external os was rather smooth while the detached border was irregular. Microscopic examination showed marked extravasation of blood into the tissue substance. There was little cellular structure present, and only in an occasional area was any glandular structure found.

After delivery the patient was given a transfusion of 400 c.c. of blood.

On the first post-partum day, she was stuperous, respirations 40 per minute; pulse, 104 and of good quality; and temperature, 102.4° F. An x-ray of the chest revealed small areas that were interpreted as infarcts or atelectasis. Oxygen was given by nasal catheter.

The patient was critically ill for four days and then began to improve slowly. On Sept. 2, 1939, a repeat x-ray of the chest showed clearing of the areas previously involved. Treatment for the most part was supportive, involving fluids, transfusions, and oxygen. Eighty grains of sulfanilamide were given for two days, and then reduced to 60 gr. for two days, but then discontinued because of marked anemia.

Three weeks after admission the patient was well enough to be discharged. Speculum examination revealed a nonsymptomatic rectovaginal fistula on the left wall of the vagina about 1 cm. above the mucocutaneous junction. The cervix was raw in appearance, bled easily, and was practically flush with the vaginal vault. The posterior lip presented three linear grooves running anteroposteriorly. The fundus was about 3 cm. above the symphysis.

The patient was seen again six weeks later, at which time the cervix looked scarred and gray and still bled very easily. Skin tests revealed negative tuberculin and Ducrey reactions. Frei reaction remained positive for ten days. She attended a venereal disease clinic regularly where she was given sulfanilamide.

The patient presented herself at the prenatal clinic on June 17, 1940, with the history of amenorrhea since Feb. 18, 1940. Examination of the abdomen revealed a soft tumor mass arising from the pelvis and extending to within 5 cm. of the umbilicus. Vaginal examination revealed this to be a pregnant uterus. The cervix

was firm and irregular and flush with the vaginal vault. Her pelvic measurements were I.S. 24 cm., I.C. 26 cm., E.C. 19 cm., and D.C. not reached. Outlet was ample.

The patient reported to prenatal clinic regularly. She was admitted into the hospital Oct. 3, 1940, having been in intermittent labor for a period of fifty hours, with a history of ruptured membranes fifteen hours prior to admission. She was thirty-three weeks pregnant. Five and one-half hours after admission, a boy infant weighing 3 pounds 9 ounces was delivered as a footling breech. Labor and delivery were uncomplicated and the infant was in good condition. She was discharged in good condition after a normal post-partum course. Urinalysis on admission revealed 3+ albumin, and numerous pus cells and hyaline and granular casts. She had no urinary symptoms. On discharge hyaline and granular casts were still present. The blood picture and chemistry were normal as was the kidney dilution and concentration test.

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CENTRAL PLACENTA PREVIA WITH ACCESSORY LOBE

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WE ARE presenting a rather rare anomaly of the placenta, the association of central placenta previa with placenta succenturiata. We have been unable to find a similar case in the literature.

B. L., a 26-year-old primipara, was admitted on Oct. 5, 1940, with a history of moderate vaginal bleeding, unassociated with pain, for the week prior to admission. Her last menstrual period was Jan. 11, 1940, and the expected date of confinement was Oct. 18, 1940. The patient had been married for five years, but had never been pregnant previously, despite the fact that she used no contraceptive measures. The cause of the sterility was found, upon investigation, to be due to a spermatozoal deficiency in her marital partner. The present pregnancy had been induced by artificial insemination of a donor's semen on her calculated ovulatory date, which occurred approximately between January 22 and January 24, as estimated by basal body temperatures and vaginal smears. Past medical and surgical history were essentially negative. The ante-partum course was normal. Membranes were intact.

Admission examination revealed a uterus enlarged to the size of a thirty-eight weeks' gestation, which contained a full-term fetus in the right occipitoposterior position. The fetal heart was in the right lower quadrant, with a rate of 140 and was regular. On rectal examination, the cervix was found to be one finger dilated. The vertex was high above the pelvic brim. During the examination, blood continued to ooze in small amounts from the vagina, and the patient was considered not to be in labor. Subsequent rectal examination showed a soft, thickened mass overlying the lower posterior position of the cervix. X-ray examination showed, after the instillation of sodium iodide into the urinary bladder, a wide spacing between the presenting fetal head and the concave superior border of the bladder, suggesting a central placenta previa. On the basis of this radiographic evidence, substantiating clinical impressions, abdominal termination of the pregnancy was deemed necessary.

On October 6, a low-flap transverse cesarean section was performed under local anesthesia and a living female infant, weighing 6 pounds 4 ounces was delivered. The placenta was found to consist of two distinct lobes of approximately the same

size. One lobe was located centrally, over the internal os, while the other lobe was situated over the right anterior lateral surface of the uterus in the lower uterine segment. The umbilical cord was centrally attached to the centrally located lobe, and there were several blood vessels traversing the distance between the two lobes. The patient ran a fairly comfortable postoperative course, the temperature fluctuating between 100° and 101° F. up to the ninth postoperative day, and then returning to normal. She was discharged on October 20, 14 days postoperatively, in good condition, with a healthy female infant.

MISSED ABORTION, WITH A NEGATIVE FRIEDMAN TEST, FOLLOWING MADLENER OPERATION

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FAILURE of an approved type of sterilization operation which has been properly performed is always of interest. When the pregnancy also involves diagnostic difficulties such as lack of subjective symptoms and a negative Friedman test, it probably warrants reporting.

A white woman, aged 27 years, gravida iii, para iv, was referred to Steiner Clinic by her physician, who suspected a fibromyomatous uterus with irregular bleeding. Her family history was of no significance, except one sister was in an institution for the feeble-minded. Menstruation began at the age of 14, was of the twenty-eight-day type, and lasted four days without unusual discomfort. Her first pregnancy in February, 1935, resulted in the birth of normal triplets. The second pregnancy was complicated by placenta previa with hemorrhage and was terminated by one of us (B. L. S.) by a classical cesarean section at Georgia Baptist Hospital in October, 1939. A Madlener operation was done on both tubes, using silk ligatures, and her convalescence was uneventful.

Her last normal menstrual period occurred about six months ago. There had been no period of amenorrhea, but she had experienced irregular bleeding varying in amount from "spotting" to a rather steady flow with only an occasional interval of a few days. There was no pain, change in appetite, breast signs, or increased frequency of urination. Slight nausea had been present for the past six weeks.

Examination showed nothing of interest except in the abdomen and pelvis. The low right paramedian scar was intact. A nontender, slightly movable mass arose from the pelvis and reached the abdominal wall about 7 cm. above the symphysis pubis. Bimanual examination showed a parous outlet with good muscular support. The urethra and Bartholinian glands were normal. The vagina contained a moderate amount of sanguinomucoid discharge which issued from the cervix. The cervix was soft and patulous and pointed toward the introitus. The uterus was enlarged to about 10 by 12 cm. and of somewhat softer than normal consistency. The adnexa could not be palpated and there was no tenderness in the fornices.

A diagnosis of pregnancy with threatened abortion was made but the patient demurred on account of the lack of subjective symptoms which had been quite pronounced in her previous pregnancies. A Friedman test was then done using two 7.5 c.c. doses of concentrated urine. Laparotomy on the rabbit at thirty-six hours was definitely negative (both ovaries studded with mature but unruptured follicles). The blood sedimentation rate, blood count, urinalysis, and Kahn test were normal. In view of the diagnostic evidence against pregnancy, laparotomy was advised.

At operation on Aug. 15, 1940 (G. A. W.), the uterus and abdominal scars were found to be adherent and loops of small intestine and omentum were attached to each side. The uterus was the size and consistency of a three months' pregnancy but was of nongravid appearance. No corpus luteum or mature follicles could be

found in either ovary. The Fallopian tubes showed the silk ligatures of the Madlener operation to be in situ and there was no sinus formation visible to the naked eye. A supravaginal hysterectomy was done and in spite of the temptation to study the shortened tubes, it was thought that the ovarian vascularity would be preserved best if these were not removed. An incidental appendicectomy was performed.

Pathologic Examination (Dr. E. L. Bishop).—The uterus was filled with placental tissue and contained a degenerated fetus 8 cm. long. The uterine wall was thick and fibrous but no fibromyomas were found. The endometrial surface was obscured by placental tissue.

Microscopic Examination.—Sections of the uterine wall showed thick muscle and connective tissue bundles with some edema and vascularity. No fibromyomatous formation was seen. The endometrium was of gravid type and the decidua was thick and compact. There were several small necrotic areas in the decidual layer but no massive degeneration.

Sections of the placental tissue showed marked variation in the size and shape of the villi. All were covered with epithelium. The central cores showed varying changes, some fibrous, some loose and vacuolated, but no actual necrosis. Proliferating Langhan's cells and a few syncytial giant cells were seen.

Sections of the appendix showed the lumen filled with feces and an intact mucosa. There was some increase in connective tissue in the submucosa.

Diagnosis.—Uterine fibrosis with pregnancy. Degenerative changes in placental villi and necrosis of decidua. Gross degeneration of fetus. Chronic appendicitis with stasis.

COMMENT

The Madlener sterilization operation leads all others in popularity; but its silk ligatures in the presence of crushed tissue, where they will almost invariably cut through into the mucous membrane of the tube, violate two of the accepted principles of the use of this material, and sinus formation must occur frequently. Failures are difficult to estimate but they have been reported to be as high as 5 per cent.[1] The Pomeroy-Lull operation in which catgut is used without crushing is statistically more effective, but is much newer.

The Friedman test properly done is of inestimable value in the diagnosis of a pregnancy obscured by atypical objective and subjective symptoms, but it is dependent upon the presence of functioning chorionic tissue. Missed abortion is one of its recognized limitations but fortunately is not very common. In this case parietal and visceral adhesions interfering with uterine expulsive efforts may have been an etiologic factor in the missed abortion. The complete retrogression of the corpus luteum of pregnancy was also significant.

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DIAPHRAGMATIC HERNIA COMPLICATING THE PUERPERIUM*

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(From the Services of the Chicago Maternity Center)

A HERNIA through the diaphragm occurs rarely, but, due to the position of the abnormal opening, is much more likely to be exposed to the force of increased abdominal pressure in labor than is an inguinal hernia, which is protected by the bulk of the uterus. This combination of diaphragmatic hernia and the immediate puerperium is sufficiently uncommon to merit the report of the following case: (An exhaustive survey of the literature brought to light only a single reference in the *Journal of the American Medical Association* of 1937 under "Query and Minor Note," the case of a doctor's wife whose labor and puerperium were complicated by herniation into the thorax of one-fourth of her stomach.)

Our patient, a 20-year-old white gravida ii, first presented herself when three and one-half months pregnant. Her last normal menstrual period was on Aug. 25, 1939. She was considered to be at term on June 2, 1940. The pertinent history obtained was a right inguinal herniorrhaphy at Billings Hospital in 1938, four months following a normal spontaneous delivery at Chicago Lying-in Hospital. Physical examination was essentially negative; Wassermann reaction was negative. Her pregnancy, which was of forty-three weeks' duration, was marked by excessive weight gain (29.5 pounds) and albuminuria. The labor came on June 27, 1940 and after thirteen and one-third hours terminated spontaneously in the birth of a 9-pound female baby. A midline, second degree laceration was repaired under pudendal block anesthesia.

Immediately after delivery, the patient complained of left upper quadrant pain but was otherwise comfortable and in good condition. For the next seventeen hours she had mild lower abdominal pains, at the end of which time her pulse, temperature, respirations, and blood pressure were normal. Nothing unusual was detected by careful physical examination. When next seen, about sixteen hours later, she complained of severe left upper and lower quadrant colicky pains, of having vomited 5 or 6 times, and of obstipation. Physical examination was again negative and her pulse, temperature, and respirations were still normal. The possibility of an intestinal obstruction was suggested. The patient was closely watched. Early on the third post-partum day about fifty-some hours after delivery, with temperature 98.6° F. and pulse 100, signs developed which led to a clear-cut diagnosis. There were left-sided abdominal pains, tenderness, and slight distention. Examination of the chest revealed diminished diaphragmatic excursions and decreased breath sounds on the left. Typically intestinal borborygmus was heard high in the left axilla. The vomiting had ceased but the obstipation remained. The patient was admitted to the Chicago Memorial Hospital on July 1, 1940, with the diagnosis of intestinal obstruction on the basis of left-sided diaphragmatic hernia.

She was given fluids parenterally, and her symptoms rapidly subsided. However, the next day when fluids were given orally, the pain and vomiting re-appeared. Relief was obtained from morphine and atropine, and she remained asymptomatic throughout her hospital stay. Her pulse and temperature were always normal but for the first day's elevation of 100.4° F. Laboratory findings were negative but for occult blood in the stool on July 3. The patient left voluntarily July 10, but she agreed to return at a later date for operation.

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*Presented at a meeting of the Chicago Gynecological Society, December 20, 1940.

INTERSTITIAL TWIN PREGNANCY*

E. W. FISCHMANN, M.D., CHICAGO, ILL.

MRS. S. S., 39 years old, one child 22 years old, living and well, no other pregnancies, menses of the twenty-eight-day type, regular up to July 1, 1940, on Aug. 17, 1940, experienced moderate abdominal cramps unassociated by nausea and vomiting, frequent urination and moderate vaginal bleeding which had continued up to the time of examination.

Sept. 3, 1940, examination revealed patient in good physical condition, no abdominal rigidity, uterus was slightly enlarged and softened and the right ovary was palpable. Aschheim-Zondek test was weakly positive. A diagnosis of probable intrauterine pregnancy was made.

Patient returned on Sept. 30, 1940, and upon examination the uterus was found to be somewhat smaller and firmer with a hen egg-sized elongated cystic mass on the left side, and the right ovary was palpable and cystic. Patient had a moderate reddish brown vaginal discharge. Hemoglobin was 80 per cent; 4,100,000 erythrocytes; 11,000 leucocytes.

A diagnosis of probable left-sided interstitial pregnancy was made and the patient entered the hospital, and a laparotomy was performed. Upon opening the abdominal cavity, there was about 100 c.c. of hemorrhagic fluid, and the omentum was adherent to the hemorrhagic enlargement of the left horn of the uterus. A supravaginal hysterectomy with bilateral salpingo-oophorectomy was performed. The patient made an uneventful recovery.

Pathologic Report.—Specimen consisted of a corpus uteri, both tubes, and both ovaries.

The corpus uteri measured 8 by 6 by 5½ cm. It was deformed by a soft mass occupying its left horn; this mass measured about 4½ cm. in diameter, and on cut section contained clotted blood in the midst of which was a twin pregnancy, the length of the fetuses being 10 mm.

Both tubes were patent and of normal size except the interstitial portion of the left one which took part in the mass described above.

The ovaries were normal except that the right one contained a hemorrhagic corpus luteum cyst, measuring 5 mm. in diameter.

58 EAST WASHINGTON STREET

A THREE-WAY SCISSORS TYPE VAGINAL BIOPSY PUNCH†

HARRY O. MARYAN, M.S., M.D., CHICAGO, ILL.

IN A previous paper[1] I described my scissors type cervical punch for obtaining adequate biopsies of the cervix uteri. Subsequently I have also found this type of a punch with its modified jaws to be applicable for obtaining vaginal biopsies with ease.

This vaginal punch (Fig. 1) consists of a pair of handles with a spring and roller attachment, a shaft with a mortise or Bruening lock, and male and female blades. The shafts are long enough having an overall measurement of 18.5 cm., so that they can reach well into the vaginal vault. Beneath the female jaw there is attached the removable basket spring which retains the specimen. The handles are so aligned that the object is always in direct line of vision. The spurs on the handles prevent the hand from slipping when pressure is applied. The jaws present

*Presented at a meeting of the Chicago Gynecological Society, January 17, 1941.
†Presented at a meeting of the Chicago Gynecological Society, December 20, 1940.

a T-shaped end measuring 12 mm. in width. The lower or female jaw has a rectangular slotted opening that measures 7 mm. in width and 3 mm. in length, and the upper, solid, male rectangular punch blade measures about 6.75 mm. in width and 2.75 mm. in length. The male blade is invaginated into the female jaw by means of a lower shaft which is slotted to insure proper aligning of the jaws. The jaws may be opened wide like a scissors ordinarily, but for biopsy purposes they are opened 12.5 mm. or 0.5 inch.

This punch is capable of obtaining biopsies from either the right lateral wall or the left lateral wall, or the vault of the vagina. The punch takes a small side bite of folded tissue which opens to a size 3 mm. square, or a bite of folded tissue from the vault which measures 7 mm. in width and 6 mm. in length. These specimens include all the layers of the vaginal mucosa, and are about 1.5 mm. thick.

Fig. 1.—Three-way scissors type vaginal biopsy punch. (Courtesy of V. Mueller and Company.)

Technique.—The usual bivalve vaginal speculum is inserted so that the vaginal walls are a little lax. The site of the biopsy is sterilized by the usual antiseptics and then is injected with a small amount of 0.5 per cent novocaine producing a small bleb. The syringe and needle remain in situ thereby steadying and elevating the biopsied area, so that the biopsy may be easily obtained by applying the side of the three-way vaginal biopsy punch.

Very little pressure is necessary to obtain these specimens. As a rule with this procedure, especially with the 3 mm. square specimens, there is very little bleeding or pain. The specimen may be easily removed by picking it out with a tissue forceps or removing it with the detachable spring basket.

I wish to express my appreciation to Dr. M. Edward Davis for his suggestions.

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30 North Michigan Avenue

Society Transactions

NEW YORK OBSTETRICAL SOCIETY

MEETING OF DECEMBER 10, 1940

The following papers were presented:

Cord Transfusions at the Time of Delivery With Suggestions as to Their Use. Dr. Harry W. Mayes.

Vitamin K Administered to the Mother During Labor as a Prophylaxis Against Hemorrhage in the Newborn Infant. Drs. Alfred C. Beck, E. Stewart Taylor, and R. F. Colburn. (For original article, see page 765.)

Urinary Stress Incontinence. Its Relation to Cystocele and Lacerations of the Pelvic Floor. Dr. J. W. Davies. (By invitation.)

CHICAGO GYNECOLOGICAL SOCIETY

MEETING OF DECEMBER 20, 1940

The following papers were presented:

Diaphragmatic Hernia Complicating the Puerperium. Drs. S. T. DeLee and B. I. Gilson. (For original article, see page 904.)

Jelly Contraceptives. Drs. Irving F. Stein, Melvin R. Cohen, and Rita Nielsen, R.N. (For original article, see page 850.)

Sickle-Cell Anemia in Pregnancy. Drs. Alfred J. Kobak, P. J. Stein, and A. F. Daro. (For original article, see page 811.)

A Three-Way Scissors Type Vaginal Biopsy Punch. Dr. Harry O. Maryan. (For original article, see page 905.)

MEETING OF JANUARY 17, 1941

The following papers were presented:

A Study of the Corpora Lutea and the Endometria in Patients With Uterine Fibroids. Drs. John I. Brewer and Harold O. Jones. (For original article, see page 733.)

Nerve Tumors of the Female Generative Organs. Dr. Robert Meyer, Minneapolis, Minn. (By invitation.)

Interstitial Twin Pregnancy. Dr. E. W. Fischmann. (For original article, see page 905.)

BROOKLYN GYNECOLOGICAL SOCIETY

MEETING OF DECEMBER 6, 1940

The following papers were presented:

Anoxia Following Nitrous Oxide Anesthesia for Labor. Drs. Thomas R. Turino and H. R. Merwarth. (For original article, see page 843.)

Further Observation of Human Refrigeration. Dr. Temple Fay (by invitation).

OBSTETRICAL SOCIETY OF BOSTON

MEETING OF JANUARY 21, 1941

The following paper was presented:

The Technique and End Results of Elective Fundal Cesarean Section. Dr. Edward A. Schumann.

MEETING OF FEBRUARY 18, 1941

The following papers were presented:

The Advantages of Conservative Obstetrics as Shown by Examination Six Weeks Post Partum. Drs. H. Bristol Nelson and Daniel Abramson. (For original article, see page 800.)

Statistics for Cesarean Section Throughout the State During 1939. Dr. Robert L. DeNormandie.

PITTSBURGH OBSTETRICAL AND GYNECOLOGICAL SOCIETY

MEETING OF DECEMBER 2, 1940

The following papers were presented:

Intestinal Obstruction Complicating Pregnancy. Drs. C. J. Barone, H. A. Power and C. L. Kuhn (by invitation). (For original article, see page 890.)

Pregnancy Complicating Breast Carcinoma. Drs. H. A. Power and J. M. Cook (by invitation).

ST. LOUIS GYNECOLOGICAL SOCIETY

MEETING OF DECEMBER 12, 1940

The following papers were presented:

Endometriosis of the Lungs. Dr. John E. Hobbs, and A. R. Bortnick. (For original article, see page 832, November, 1940 issue.)

Pregnancy in Uterus Didelphys. Dr. Joseph A. Hardy, Jr. (For original article, see page 885.)

Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

Selected Abstracts

Pathology of Pregnancy

Spector, H. I.: Marital Tuberculosis, Am. Rev. Tuberc. **40**: 147, 1939.

Marital tuberculosis in this paper designates clinical tuberculosis in both husband and wife, not implying that the disease has been transmitted from the one to the other.

Spector's study considers available literature, 208 questionnaires answered by physicians in the U. S. and various foreign countries but is chiefly based on the histories of 210 tuberculous couples found among over eleven thousand cases of tuberculosis reported to the St. Louis Health Division.

Some of the final conclusions drawn by the author are the following: Marital tuberculosis is not as infrequent as is generally believed, amounting to 3.8 per cent of the reported cases of tuberculosis in married people. The majority of physicians answering the questionnaires approve of marriage between tuberculous individuals and between a tuberculous and nontuberculous one. The majority of phthisiologists permit their arrested married tuberculous patients to have children.

HUGO EHRENFEST.

Dodds, Gladys H.: Chronic Nephritis in Pregnancy, Proc. Roy. Soc. Med. **33**: 737, 1940.

Chronic glomerular nephritis is predominantly a disease of young people, yet it is rarely associated with pregnancy. The incidence at the University College Hospital (London) was 1 in 1,100 deliveries. Clinical diagnosis of the disease, especially differentiation from a chronic hyperpiesis, is difficult, often takes much time, occasionally a year or more after delivery.

Remote prognosis for the mother is usually regarded as extremely unfavorable. If it is true that pregnancy is always liable to cause an exacerbation of the disease and shortens the patient's life, then obviously the best course to adopt is to terminate the pregnancy as soon as it is diagnosed. Only in exceptional cases gestation could be continued under proper medical treatment until the fetus has reached viability.

HUGO EHRENFEST.

Bertino, Steffano: Treatment of Malaria in Pregnancy with Tartrated Antimony, Ginecologia **5**: 362, 1939.

The author treated 4 patients with acute and 6 with chronic malaria during pregnancy and the puerperium with intravenous administration of 1 per cent solution of tartrated antimony.

In all cases the disease was easily controlled. The hemoglobin increased 10 to 40 per cent and good health returned. One patient experienced vomiting and a few moments of severe coughing during the administration of the drug. The patient also showed restriction of urinary output. These untoward symptoms compelled interruption of treatment with tartrated antimony and resumption of administration of quinine, intramuscularly and by mouth.

Eight of the 10 patients were able to nurse their infants. Live babies were obtained in 9 cases. The end result of labor in one case is not reported. The initial weight loss of the infants was regained in normal length of time.

Of the 6 cases of chronic malaria the drug was first used in the second, sixth, and the seventh month, in one each, and during the ninth month in the 3 remaining cases. In the 4 patients with acute malaria, the drug was given in the puerperium in 2 patients and in the fifth and sixth months of pregnancy in the other 2 patients.

The total dosage varied from 52 c.c. to 230 c.c. The author does not offer any specific routine for use of the drug except to mention that in 2 patients it was given in 2 to 3 courses, each of 4 to 5 injections; 7 c.c. in each of the first course, and 13 c.c. in each of the last course in one case; and daily injections for 3 courses in another case, amount dependent on blood findings. The remaining patients were treated throughout the remainder of their pregnancies and, or, into their puerperium.

In 2 cases the author, immediately post partum, utilized Frey's hysterotonographic method to check the effect of the drug upon uterine tonus. He found that following intravenous injection of tartrated antimony, the uterine muscle tone was increased and slowly returned to its previous tone.

He mentions that in considering the choice and dosage of this drug during pregnancy one must take into account this increase in muscle tone and its possible effect upon the fetus. He feels, however, that his dosages were within the limits of safety.

CLAIR E. FOLSOME.

Sodeman, W. A.: Cardiac Changes in Pregnancy Unrelated to Usual Etiologic Types of Heart Disease, Am. Heart J. **19:** 385, 1940.

The author observed 73 apparently normal patients during pregnancy to ascertain what cardiac changes resulted from the gravid state. Palpitation or dyspnea or both developed in 31 and was sufficiently severe to constitute a complaint. Choking or "smothering" at night was complained of by two. Soft systolic murmurs were common and, at times, were markedly affected by posture. In 30 instances soft, short, transient, systolic pulmonic murmurs were heard. The heart was definitely beyond the midclavicular line in 12 cases; it was confirmed by x-ray examination in 10. Tachycardia was recorded graphically in 47 cases and ectopic beats in four. Edema of the ankles was present in 28. The blood pressure of every patient remained within the normal range. In 7 of the 73 patients symptoms and signs sufficient to suggest heart disease developed in the last trimester. In five of these, palpitation and dyspnea on exertion were accompanied by accentuation of the pulmonic second sound, extension of the left border of cardiac dullness beyond the midclavicular line and systolic apical murmurs, and in two by basal systolic murmurs, edema of the ankles and coarse râles at the bases of both lungs. The arterial pressure was within the normal range in all patients. In each instance delivery was uneventful, and examination during the puerperium disclosed that practically all the signs and symptoms had disappeared. So-called gestatory heart disease must be differentiated from organic heart disease as patients with the former type require no special treatment. The inclusion of patients with gestatory heart "disease" in the organic group not only causes them unnecessary expense, inconvenience, and worry but exposes them unnecessarily to added obstetric risks.

J. P. GREENHILL.

Clahr, Klein, and Greenstein: Rheumatic Heart Disease in Pregnant Women, New York S. J. M. **40:** 1242, 1940.

The establishment of the prenatal cardiac clinic at the Morrisania City Hospital has led to a threefold increase in the number of diagnosed cases of rheumatic heart disease in pregnancy. The routine treatment of cases of rheumatic heart disease in pregnancy is described.

The combination of adequate bed rest and digitalis has been the most effective means in the prevention of intra-partum and post-partum cardiac failure in rheumatic heart disease. The only maternal deaths occurred in patients who had neither adequate bed rest nor digitalis.

J. P. GREENHILL.

Giuffrida, Francesco: Fibromyomas and the Puerperal State, Rassegna d'ostet. e ginec. **49:** 18, 1940.

The author reports 11 cases of fibromyomas in gravid women occurring under his observation.

Four of the 11 patients were subjected to myomectomies while pregnant from two to three months. Two of these patients aborted the next day, one terminated with normal delivery, but proluton was used postoperatively to prevent abortion; the fourth patient was delivered vaginally at term, but the labor was complicated by placenta previa.

Four additional patients, pregnant forty days to six months, were treated by supravaginal or total hysterectomy. The three remaining patients were all delivered by laparotrachelotomy at term. Myomectomies were performed at the time of the sections.

The author concludes that with proper individualization of each case there is really little to fear from coexistent fibroids. Proluton is considered by him a valuable form of postoperative medication.

CLAIR E. FOLSOME.

Smalldon, J. L.: Survey of Mental Illness Associated with Pregnancy and Childbirth, Am. J. Psychiat. **97:** 80, 1940.

The writer studied the records of 220 women admitted to the New York Hospital, Westchester Division, because of mental illness associated with childbirth and the puerperium. These cases comprised roughly 8 per cent of the female admissions during the period (1922 to 1938) under study. Manic-depressive psychoses accounted for 107 of the cases, dementia precox for 64, psychoneurosis for 28, psychosis with psychopathic personality for 10, toxic-exhaustive psychosis for eight, a psychopathic personality with pathologic emotionality but without psychosis for two and a paranoid condition for one. Only 3.6 per cent of the cases were classified as deliriums directly attributed to the toxic-exhaustive factors of reproduction, although such factors were frequently precipitating causes in the development of rather typical manic-depressive reactions, particularly of the depressive type. Probably this difference in diagnosis may be attributed to the increasing recent tendency away from the belief that a specific psychosis occurs in the pregnant and post-partum states and toward the conception that the physical and psychic problems of childbirth do not determine the type of psychosis but merely act as exciting or precipitating agents.

The study does not corroborate the fact that a high proportion of the depressive type of manic-depressive psychoses and puerperal schizophrenias are of paranoid reaction. It rather shows a greater percentage of catatonia. The study corroborates the observations of Strecker and Ebaugh that these schizophrenic reactions frequently show pronounced manic-depressive symptoms, clouding of the sensorium and a tendency to remissions, that these cases tend to slow deterioration and that a high percentage of post-partum psychoses occur in the Jewish race. The study tends to corroborate to some degree Zilboorg's claim that the aloof, shy woman with little previous contact with men and prolonged courtship tends to develop puerperal schizophrenia. Antagonism toward the child, as expected from Zilboorg's hypothesis, was present. With few exceptions the psychoses did have their onset post partum.

J. P. GREENHILL.

Miller, H. C. and Ross, R. A.: Relation of Hypoglycemia to the Symptoms Observed in Infants of Diabetic Mothers, J. Pediat. **15:** 473, 1940.

The belief is widely held that the hypoglycemia of newborn infants whose mothers have diabetes mellitus is the cause of the cyanosis, muscular twitchings, convulsions, and, occasionally, the death of the infant. This assumption is naturally based upon the fact that hypoglycemia induced in older patients by the injection of insulin is accompanied by certain well-known symptoms which quickly disappear

when glucose is given and the blood sugar concentration thereby returned to normal. However, the authors' experience with infants born of diabetic mothers has given them reason to question whether or not the hypoglycemia so frequently observed in these infants is as significant in the production of symptoms as is generally supposed.

In the past three years six infants born to mothers with diabetes have been cared for on the Pediatric Service at Yale University from the time of birth to their discharge. All six had very low concentrations of blood sugar during the first day or two of life. In three infants symptoms and abnormal findings were present. In no case was the administration of glucose effective in relieving the symptoms. More striking than the lack of response to glucose was the fact that in each of these infants evidence of organic disease was found which better explained the symptoms and clinical course than would the hypoglycemia.

J. P. GREENHILL.

Evans, John R., and Bouslog, John S.: Intractable Heartburn of Pregnancy, Radiology **34:** 530, 1940.

In this report the authors show roentgenologic evidence of the so-called intractable heart burn of pregnancy. The etiologic factor is an esophageal orifice hernia. Due to a deficiency in embryologic development, there may be a congenital weakness of the esophageal ring, and, as in an inguinal hernia, later on in life, through trauma, or an increase in intra-abdominal pressure, a definite hernia may develop. The latter condition holds true in gravid women. The symptoms are constant and of increasing severity. The symptoms in nongravid individuals vary from vague nonspecific ones to those of abdominal or severe thoracic distress. Most patients exhibit various combinations of belching, heart burn, nausea, regurgitation, and vomiting. As pregnancy progresses the only relief obtainable is by maintenance of the upright posture. The symptoms bear no relation to the degree of gastric acidity and relatively little relief is obtained in these cases from antacids. Dilute hydrochloric acid does not aggravate the symptoms. Ulcer diets are disappointing, and the giving of salines and pyloric relaxants produce little or no change.

WILLIAM BERMAN.

Urzua, Oscar: Abdominal Wound Penetrating Gravid Uterus Injuring Fetus. Pregnancy Uninterrupted, Bol. Soc. chilena de obst. y ginec. **55:** 417, 1939.

A 32-year-old woman seven months pregnant was hospitalized. She was suffering with multiple knife wounds, through one of which, below the umbilicus, omentum and several loops of intestine protruded. At laparotomy a gravid uterus was found, having a linear 2 cm. wound in the fundus. As no blood or amniotic fluid appeared, the laceration was closed in two layers. Recovery was uneventful and the patient was discharged in nine days, experiencing a small intermittent discharge of small quantities of fluid per vaginam. Two months later she was spontaneously delivered of a live 1,560 Gm. baby. The infant was cyanotic and dehydrated. On the superior and lateral aspects of the left thigh, there was a 2 cm. linear wound, clean and open, covered by a thin transparent pellicle, showing no tendency to cicatrization. The infant died in six days, and on post-mortem examination, a hematoma was found beneath the wound, infiltrating the thigh and extending to the gluteal and lumbar regions. The author discusses the indications for laparotomy in emergencies during pregnancy.

R. J. WEISSMAN.

Thomson, A. M. Wright: Post-Partum Retinal Arterial Obstruction Associated With Hemiplegia, Brit. M. J. **1:** 387, 1940.

The author reports a case of retinal arterial obstruction accompanied by contralateral hemiplegia following the termination of pregnancy. The eye was permanently damaged but the hemiplegia disappeared rather rapidly. The writer suggests

that thrombosis of the pituitary artery with protrusion of the clot into the lumen of the internal carotid artery occurred. The collapse occurring after delivery slowed circulation and allowed a fresh clot to form in the ophthalmic and the middle cerebral artery. The clot in the middle cerebral artery was probably not complete and permitted the disappearance of the hemiplegia.

FRED L. ADAIR AND GEORGE BOHLENDER.

Pearce, T. Vibert: Childbirth After Presacral Neurectomy, Brit. M. J. 1: 87, 1940.

The literature on pregnancy following presacral neurectomy is reviewed briefly, and the author presents a case of his own. He concludes that this operation has no deleterious influences on pregnancy and labor and that in a small proportion of the cases the first stage of labor is rendered painless and rapid.

FRED L. ADAIR AND GEORGE BOHLENDER.

Russ, Witten B.: The Maintenance of Pregnancy in the Human After the Removal of Both Ovaries, Ann. Surg. 111: 871, 1940.

The author reports a case in which pregnancy continued after bilateral oophorectomy. The patient was a multipara who developed a torsion of the left adnexa in her second month of gestation. The right adnexa had been removed previously. The patient was given 1 c.c. of progestin on the second postoperative day, and this was continued every other day up to the end of the fourth month. The patient was delivered of a normal, eight-pound, male child. The case is reported as interesting chiefly because of the general impression that abortion is almost certain to result from the loss of both ovaries during pregnancy, especially during the first three months.

WILLIAM BERMAN.

Sadowsky, A.: Twin Pregnancy (A Discourse on Pathology), Monatschr. f. Geburtsh. u. Gynäk. 110: 81, 1940.

At the Hadassah-Rothschild Hospital (Jerusalem) in a series of 11,214 deliveries, Sadowsky found 161 twin pregnancies. Analysis of these cases showed that in twin pregnancies there is a greater tendency to toxemias, especially eclampsia, an increased incidence of abortions and premature labors, a higher percentage of operative deliveries, an increased maternal morbidity, a greater number of intrauterine fetal deaths, and a higher infant mortality during the first week of life.

J. P. GREENHILL.

Items

American Board of Obstetrics and Gynecology

The general oral and pathological examinations (Part II) for all candidates (Groups A and B) will be conducted at Cleveland, Ohio, by the entire Board from Wednesday, May 28, to Monday, June 2, 1941, inclusive, prior to the opening of the annual meeting of the American Medical Association in Cleveland.

The Board requests that all prospective candidates who plan to submit applications in the near future request and use the new application form which has this year been inaugurated by the Board. The Secretary will be glad to furnish these forms upon request, together with information regarding Board requirements. Address Dr. Paul Titus, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

This Board will hold its annual dinner for Diplomates, and others interested in the work of the Board, on Wednesday evening, June 4, 1941, at the Wade Park Manor Hotel, Cleveland, Ohio, immediately following the close of the Part II examinations. Diplomates certified at the preceding days' examinations will be introduced personally, and there will be several speakers.

Tickets at $3.25 each may be obtained from Dr. Joseph L. Baer, chairman, 104 S. Michigan Avenue, Chicago, Illinois, or at the Registration Desk during the examination period.

Directory of Medical Specialists

A second edition of the Directory of Medical Specialists has been authorized by the Advisory Board for Medical Specialties, to be ready for distribution in February, 1942, with its contents complete to January first.

This Directory is the official publication of the Advisory Board, and will list the names of approximately 18,000 diplomates of the fifteen American Boards examining candidates for certification in the specialties. This is an increase of 4,000 over the first edition issued early in 1940.

The geographic grouping will give completely revised biographic data about each diplomate; there is an alphabetic index with addresses and specialty designations; and the plan of organization, officers, and examination requirements of each American Board are fully outlined in their various sections.

The biographic data of diplomates will not only be revised to date, but also will include much new information not found in the first edition. Details of formal training is one of these, and military appointments now held is another.

Only those who have been formally certified by one of the American Boards can have their names included, and all of these are included, there being no charge or obligation other than certification for such listings.

The official nature of this Directory makes it invaluable as a reference book. It may be used generally for the referring of patients to distant communities; for the information of Medical Society officers; for gaining detailed knowledge about qualified specialists throughout the United States and Canada; for the obtaining of detailed information about the American Boards; and for many other purposes.

The first edition had a wide distribution not only throughout the medical profession as well as medical and other public libraries, but also among insurance companies and business firms dealing with physicians. Nevertheless, it is not a commercial undertaking as the Directory contains no advertising material, is underwritten by the Advisory Board and actually received subsidizing support so that it could be distributed as near to cost as possible.

Questionnaires for biographic data are now being mailed out with order forms. The Secretary of each Board urges that every diplomate return his questionnaire form as quickly as possible, and he is urged also to support this project of the American Boards by his subscription to the Directory. A substantially reduced rate is offered for prepublication orders, as the size of the printing is based largely on advance subscriptions.

The publication is issued through the Columbia University Press of New York. The Secretary of each American Board serves on the Advisory Editorial Board, and Paul Titus, M.D., 1015 Highland Building, Pittsburgh, Pennsylvania, of the American Board of Obstetrics and Gynecology, is the Directing Editor.